Hepatitis C Virus

A 3-in-1 Medical Reference

Medical Dictionary

Bibliography &

Annotated Research Guide

to Internet References

ICON Group International, Inc.

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A Medical Dictionary, Bibliography, and Annotated Research Guide to Internet References

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FORWARD

In March 2001, the National Institutes of Health issued the following warning: "The number of Web sites offering health-related resources grows every day. Many sites provide valuable information, while others may have information that is unreliable or misleading."[1] Furthermore, because of the rapid increase in Internet-based information, many hours can be wasted searching, selecting, and printing. Since only the smallest fraction of information dealing with hepatitis C virus is indexed in search engines, such as **www.google.com** or others, a non-systematic approach to Internet research can be not only time consuming, but also incomplete. This book was created for medical professionals, students, and members of the general public who want to know as much as possible about hepatitis C virus, using the most advanced research tools available and spending the least amount of time doing so.

In addition to offering a structured and comprehensive bibliography, the pages that follow will tell you where and how to find reliable information covering virtually all topics related to hepatitis C virus, from the essentials to the most advanced areas of research. Public, academic, government, and peer-reviewed research studies are emphasized. Various abstracts are reproduced to give you some of the latest official information available to date on hepatitis C virus. Abundant guidance is given on how to obtain free-of-charge primary research results via the Internet. **While this book focuses on the field of medicine, when some sources provide access to non-medical information relating to hepatitis C virus, these are noted in the text.**

E-book and electronic versions of this book are fully interactive with each of the Internet sites mentioned (clicking on a hyperlink automatically opens your browser to the site indicated). If you are using the hard copy version of this book, you can access a cited Web site by typing the provided Web address directly into your Internet browser. You may find it useful to refer to synonyms or related terms when accessing these Internet databases. **NOTE:** At the time of publication, the Web addresses were functional. However, some links may fail due to URL address changes, which is a common occurrence on the Internet.

For readers unfamiliar with the Internet, detailed instructions are offered on how to access electronic resources. For readers unfamiliar with medical terminology, a comprehensive glossary is provided. For readers without access to Internet resources, a directory of medical libraries, that have or can locate references cited here, is given. We hope these resources will prove useful to the widest possible audience seeking information on hepatitis C virus.

The Editors

[1] From the NIH, National Cancer Institute (NCI): **http://www.cancer.gov/cancerinfo/ten-things-to-know**.

CHAPTER 1. STUDIES ON HEPATITIS C VIRUS

Overview

In this chapter, we will show you how to locate peer-reviewed references and studies on hepatitis C virus.

The Combined Health Information Database

The Combined Health Information Database summarizes studies across numerous federal agencies. To limit your investigation to research studies and hepatitis C virus, you will need to use the advanced search options. First, go to **http://chid.nih.gov/index.html**. From there, select the "Detailed Search" option (or go directly to that page with the following hyperlink: **http://chid.nih.gov/detail/detail.html**). The trick in extracting studies is found in the drop boxes at the bottom of the search page where "You may refine your search by." Select the dates and language you prefer, and the format option "Journal Article." At the top of the search form, select the number of records you would like to see (we recommend 100) and check the box to display "whole records." We recommend that you type "hepatitis C virus" (or synonyms) into the "For these words:" box. Consider using the option "anywhere in record" to make your search as broad as possible. If you want to limit the search to only a particular field, such as the title of the journal, then select this option in the "Search in these fields" drop box. The following is what you can expect from this type of search:

- **Association Between Hepatitis C Virus Infection and Type 2 Diabetes Mellitus: What Is the Connection? (editorial)**

  Source: Annals of Internal Medicine. 133(8): 650-652. October 17, 2000.

  Contact: Available from American College of Physicians. American Society of Internal Medicine. 190 North Independence Mall West, Philadelphia, PA 19106-1572. Website: www.acponline.org.

  Summary: Chronic **hepatitis C virus** (HCV) infection and type 2 diabetes mellitus cause devastating long term complications in a significant minority of patients affected with these diseases. This editorial explores the potential link between these two disorders, noting that chronic HCV infection may cause cirrhosis (liver scarring), which, through insulin resistance, predisposes patients to diabetes mellitus. The author reviews a dozen

studies that look at this connection, then introduces a research study published in the same journal issue as the editorial, which provides strong evidence for the association between HCV infection and type 2 diabetes mellitus. This latter study demonstrates that persons with HCV infection were more than three times more likely to have type 2 diabetes mellitus than those without HCV infection. Alcohol abuse did not seem to link the two disorders in this study. The editorial author addresses some of the potential limitations to this study, and suggests additional research that may further clarify the connection between the two diseases. The editorial concludes that the association between chronic HCV infection and type 2 diabetes mellitus seems genuine. However, numerous questions must still be addressed, most notably those regarding the nature of the link between the disorders. 19 references.

- **Long-Term Impact of Renal transplantation on Liver Fibrosis During Hepatitis C Virus Infection**

  Source: Gastroenterology. 123(5): 1494-1499. November 2002.

  Contact: Available from W.B. Saunders Company. 6277 Sea Harbor Drive, Orlando, FL 32887-4800. (800) 654-2452. Website: www.gastrojournal.org.

  Summary: During **hepatitis C virus** (HCV) infection, liver fibrosis progression after renal (kidney) transplantation remains controversial. This article reports on a cohort study that compared liver histopathologic features during HCV infection between kidney transplant recipients and matched groups of hemodialysis patients or controls without renal disease and untreated for HCV> Each kidney transplant recipients (group 1, n = 30) was matched at first liver biopsy (LB) using the main factors known to influence progression of fibrosis, with one HCV hemodialyzed patient (group 2, n = 30) and one HCV-infected patients (nonhemodialyzed, nontransplanted; group 3, n = 30). The rate of fibrosis progression per year between the first and second liver biopsies was significantly lower in group 1 than group 3. The authors conclude that liver fibrosis progression is low in most HCV-infected kidney transplant recipients with moderate liver disease at baseline. 3 tables. 21 references.

- **Hepatic Steatosis in Chronic Hepatitis C Virus Infection: Prevalence and Clinical Correlation**

  Source: Journal of Gastroenterology and Hepatology. 16(2): 190-195. February 2001.

  Contact: Available from Blackwell Science. 54 University Street, Carlton South 3053, Victoria, Australia. +61393470300. Fax +61393475001. E-mail: Rob.Turner@blacksci-asia.com.au. Website: www.blackwell-science.com.

  Summary: Hepatic steatosis (fatty liver) is a histological characteristic in patients with chronic **hepatitis C virus** (HCV) infection. This article reports on a study undertaken to evaluate the prevalence of hepatic steatosis in Chinese patients with chronic hepatitis C, and to look for possible correlation with various histopathological changes and to look for possible correlation with various clinical and pathologic variables. The study included 106 patients; patients with alcoholism or diabetes were excluded. Of the 106 patients with chronic hepatitis C, 55 patients (52 percent) had hepatic steatosis. Patients with hepatic steatosis had higher body mass index, and a higher incidence of obesity compared with patients without hepatic steatosis. No significant differences in serum HCF RNA titer and HCF genotype or the response to interferon therapy were noted between the two groups. Histological analysis showed patients with hepatic steatosis had a significantly higher mean fibrotic (scarring) score than patients without hepatic steatosis. There were no significant differences in the severity of necroinflammation, the

presence of lymphoid aggregation or follicle or bile duct damage between the two groups. Multivariate logistic regression analysis showed that independent predictors associated with hepatic steatosis were obesity or a histology fibrotic score of greater than 2.2. 4 tables. 34 references.

- **Oral Microbiology and Oral Medicine: Hepatitis C Virus and Oral Disease: A Critical Review**

  Source: Oral Diseases. 5(4): 270-277. October 1999.

  Contact: Available from Stockton Press, 49 West 24th Street, New York, NY 10010. (212) 627-5757 or (800) 221-2123; Fax (212) 627-9256.

  Summary: Hepatitis C virus (HCV) infection is widespread, with an estimated 3 percent of the world population infected. Acute infection is usually mild but chronic disease develops in as many of 70 percent of patients, of whom at least 20 percent will eventually develop cirrhosis. Infection with HCV may have effects on various organs other than the liver and has been associated with a variety of extrahepatic (outside the liver) manifestations. This review article discusses the evidence implicating HCV in the etiology (cause) of two oral conditions, namely Sjogren's syndrome (SS) and oral lichen planus (OLP). The authors discuss the association of HCV with salivary gland abnormalities in two scenarios: the severe sialadenitis (salivary gland infection) seen in SS and the fact that patients with HCV infection commonly have a mild form of lymphocytic sialadenitis that, morphologically, closely resembles that of primary SS. However, even though the involvement of HCV in sialadenitis is biologically plausible, the exact role of the virus in the development of the disorder has yet to be determined. Whether HCV is one of the exogenous triggers that activate the immune system, resulting in the cascade of events leading to OLP, also remains as yet unconfirmed. If so, it has to be clarified whether HCV acts locally by influencing keratinocyte function or whether host immune responses to HCV are responsible for the development of OLP. 2 tables. 126 references.

- **Natural History of Hepatitis C Virus Infection: Host, Viral, and Environmental Factors**

  Source: JAMA. Journal of the American Medical Association. 284(4): 450-456. July 26, 2000.

  Summary: Hepatitis C virus (HCV) infection may resolve (viral clearance), persist without complications, or cause end stage liver disease (ESLD). The frequency and determinants of these outcomes are poorly understood. This article reports on a study undertaken to assess the incidence and determinants of viral clearance and ESLD among persons who acquired HCV infection from injection drug use. The community based prospective cohort study used enrollment in 1988 to 1989, with a followup of 8.8 years. The study featured a total of 1,667 persons aged 17 years or older with a history of injection drug use and an HCV antibody positive test result during followup. Viral clearance was observed in 90 persons who were compared with 722 with persistent viremia, while the viremia of 107 was not resolved. Viral clearance occurred more often in nonblacks and those not infected with human immunodeficiency virus (HIV). Forty cases of ESLD were observed throughout followup. In analysis, the risk of ESLD was higher for persons aged 38 years or older at enrollment and who reported ingestion of more than 260 g of alcohol per week. Of 210 patients without ESLD randomly selected for biopsy, only 2 had cirrhosis. The authors conclude that although HCV infection can be self limited or associated with ESLD, the majority of adults have persistent viremia,

without clinically demonstrable liver disease. Further research is needed to explain the less frequent clearance of HCV infection among black persons and to improve utilization of treatment for those infected in the context of injection drug use. 3 tables. 44 references.

- **Hepatitis C Virus Infection**

  Source: New England Journal of Medicine. 345(1): 41-52. July 5, 2001.

  Summary: Hepatitis C virus (HCV) infects an estimated 170 million persons worldwide and thus represents a viral pandemic, one that is five times as widespread as infection with HIV. This article reviews recent advances in understanding the pathogenesis (development) of the infection and improvements in treatment options. The author notes that the institution of blood screening measures in developed countries has decreased the risk of transfusion associated hepatitis to a negligible level, but new cases continue to occur mainly as a result of injection drug use and, to a lesser degree, through other means of percutaneous or mucous membrane exposure. Progression to chronic disease occurs in the majority of HCV infected persons, and infection with the virus has become the main indication for liver transplantation. HCV infection also increased the number of complications in persons who are coinfected with HIV. The authors conclude that the best hope for a solution to the epidemic of HCV infection is the development of an effective vaccine. Although the recent demonstration of apparent immunologic clearance of virus in some persons with acute infection provides hope that a vaccine may someday be developed, it is not likely to be available soon. For those who are already infected with HCV, new therapeutic approaches can be expected in the future. Persons who have no response to therapy and who have a high risk of imminent progression to decompensated liver disease might benefit from therapies (such as interleukin 10) that halt disease progression until better therapies become available. 3 figures. 3 tables. 106 references.

- **Hepatitis C Virus (HCV) Infection and Liver-Related Mortality: A Population-Based Cohort Study in Southern Italy**

  Source: International Journal of Epidemiology. 29(5): 922-927. October 2000.

  Contact: Available from Oxford University Press. Journals Subscription Department, Great Clarendon Street, Oxford OX2 6DP, UK. 44 (0)1865 267907. Fax 44 (0)1865 267485.

  Summary: Hepatitis C virus (HCV) is a common cause of chronic liver diseases but the degree to which these diseases contribute to liver related mortality (death) is not well established. This article reports on a study undertaken to estimate the absolute and relative effects of HCV infection on liver related mortality. A population random sample of 2,472 subjects aged greater than 30 years was enrolled and followed up from 1985 to 1996. At enrollment, a structured interview and a clinical evaluation were performed. Serum samples were tested using HCV ELISA and RIBA HCV. Crude overall and liver related mortality rates were 7.66 and 0.9 per 10 cubed person years, respectively. For HCV infection effect, incidence rate ratio and difference (per 10 cubed person years), risk ratio and difference were 27.5 and 0.06, respectively. All measures were adjusted for age at death, sex, and daily alcohol intake. The results show a strong relative but weak absolute effect of HCV infection on liver related mortality in the 10 year period considered. The authors conclude with a brief discussion of the potential impact of interferon and other antiviral therapies. 4 tables. 46 references.

- **Mother-to-infant Transmission of Hepatitis C Virus**

  Source: Hepatology. 34(2): 223-229. August 2001.

  Contact: Available from W.B. Saunders Company. 6277 Sea Harbor Drive, Orlando, FL 19106-3399. (800) 654-2452 or (407) 345-4000.

  Summary: Hepatitis C virus (HCV) is acquired through transfusion of infected blood or blood products or through routes not related to transfusion, classified as community acquired disease. The rate of mother to infant HCV transmission is critical to predicting the burden of HCV infection in future generations (particularly after the implementation of blood product screening in 1991). The factors that determine whether or not an infant actually becomes infected need to be identified. This article reports on a review of published studies (n = 77, 1992 to 2000) of mother to infant transmission of HCV. The number of anti HCV positive mother-infant pairs ranged from 10 to 1,338 per study. The articles in this review reported a total of 363 cases of mother to infant transmission; the majority of studies originated from Italy and Japan. The prevalence of anti HCV positive women among all pregnant women varied widely across these studies, from 0.6 percent to 95.4 percent, reflecting the heterogeneity of the populations studied. For example, the 3 studies with highest prevalence were limited to intravenous drug users (IVDU). The reported rate of mother to infant HCV transmission ranged from 0 to 35 percent among children born to anti HCV positive women. HCV transmission patterns may differ among certain groups and, indeed, the definition of mother to infant transmission differed among studies. The rate of mother to infant HCV transmission appears increased among women coinfected with human immunodeficiency virus (HIV) compared with women without HIV infection. Between infants delivered vaginally versus by Cesarean section, overall rates of mother to infant transmission were similar. Overall rates of mother to infant transmission between breast fed and non breast fed infants were similar. Suggested viral factors such as genotype and viral titer were not consistently measured across studies; hence, their roles as significant risk factors in mother to infant transmission remain to be conclusively shown. Inconsistent follow up among studies resulted in only sporadic description of clinical outcome for infected infants. The authors conclude that, based on observational data from these 77 cohort studies, maternal risk factors for increased mother to infant transmission of HCV include coinfection with HIV, history of IVDU, and maternal viremia greater than 10 to the 6th power copies per milliliter. 2 tables. 102 references.

- **Screening for Hepatitis C Virus Infection: A Review of the Evidence for the U.S. Preventive Services Task Force**

  Source: Annals of Internal Medicine. 140(6): 465-479. March 2004.

  Summary: Hepatitis C virus 9HCV) is the most common bloodborne pathogen in the United States and is an important cause of patient morbidity and mortality, but it is unclear whether screening to identify asymptomatic infected persons is appropriate. This article reports on a review of the evidence on risks and benefits of screening for HCV infection. The authors reviewed controlled studies of screening and antiviral therapy and observational studies on other interventions, risk factors, accuracy of antibody testing, work-up, harms of biopsy, and long-term outcomes. There are no published trials of screening for HCV infection. Approximately 2 percent of U.S. adults have HCV antibodies, with the majority having chronic infection. Data are insufficient to determine whether treatment improves long-term outcomes. The authors conclude that data are inadequate to accurately weight the overall benefits and risks of screening in otherwise healthy asymptomatic adults. 8 tables. 181 references.

- **Hepatitis C Viral Infection: Modelling the Hepatitis C Virus Epidemic in Australia**

  Source: Journal of Gastroenterology and Hepatology. 14(11): 1100-1107. November 1999.

  Contact: Available from Blackwell Science. 54 University Street, Carlton South 3053, Victoria, Australia. +61393470300. Fax +61393475001. E-mail: Rob.Turner@blacksci-asia.com.au. Website: www.blackwell-science.com.

  Summary: In Australia, to the end of 1997, more than 110,000 people have been diagnosed with **hepatitis C virus** (HCV) antibodies and reported to State or Territory surveillance systems. The available data indicate that the overwhelming majority (around 80 percent) of people with HCV antibodies were infected through injecting drug use. This article reports on the development of models of the HCV epidemic in Australia, which were based on estimates of the pattern of injecting drug use in Australia. Estimates of HCV infections due to injecting drug use thus obtained were then adjusted to allow for HCV infections resulting from other transmission routes. Projections of cirrhosis (liver scarring) and hepatocellular carcinoma (HCC, or liver cancer) resulting from HCV were obtained by combining modelled HCV incidence with estimates of the progression rates to these outcomes. Based on the models, it was estimated that there were 196,000 (lower and upper limits of 149,000 and 234,000) people in Australia living with HCV antibodies at the end of 1997. HCV incidence in 1997 was estimated to be 11,000 (8,500 to 13,500). It was estimated that 8,500 (4,000 to 13,000) people were living with HCV related cirrhosis in 1997 and that there were 80 (40 to 125) incident cases of HCV related HCC. Model based estimates were broadly consistent with other sources of information on the HCV epidemic in Australia. These models suggest that the prevalence of HCV related cirrhosis and the incidence of HCV related HCC will more than double in Australia by 2010. 4 figures. 5 tables. 30 references.

- **Hepatitis C Virus Six Years On**

  Source: Lancet. 344(8935): 1475-1479. November 26, 1994.

  Summary: In this article, the authors review the activities of researchers and clinicians in the years since the **hepatitis C virus** (HCV) was cloned in 1988. They note that the years have brought characterization of the complete virus, knowledge of its genetic variability, three generations of diagnostic antibody tests, and increasing experience of viral nucleic acid detection, epidemiology, and antiviral treatment. They discuss in detail the development of interferon treatment in hepatitis C, including its use to prevent progression of the early or acute stage to chronic hepatitis C. 3 figures. 35 references. (AA-M).

- **Hepatitis C Virus in the Setting of Transplantation**

  Source: Seminars in Liver Disease. 15(1): 92-100. February 1995.

  Contact: Available from Thieme Medical Publishers, Inc. 381 Park Avenue South, New York, NY 10016. (800) 782-3488.

  Summary: In this review article, the authors address certain aspects of transplantation and **hepatitis C virus** (HCV). Topics include pretransplant assessment; the diagnosis of HCV infection in the transplant setting; the natural history of HCV infection in liver transplants; HCV in the nonliver transplant setting; and implications for the pathogenesis of HCV. The authors note that the natural history of infection following transplantation will continue to evolve as the duration of followup in transplanted patients increases. Natural history data is important to the interpretation of intervention trials involving such drugs as IFN and ribavirin. 62 references.

- **Risk Factors for Hepatitis C Virus Infection in United States Blood Donors**

  Source: Hepatology. 31(3): 756-762. March 2000.

  Contact: Available from W.B. Saunders Company. 6277 Sea Harbor Drive, Orlando, FL 19106-3399. (800) 654-2452 or (407) 345-4000.

  Summary: Injection drug use (IDU) is a known risk factors for **hepatitis C virus** (HCV) infection, but the strength of other parenteral and sexual risk factors is unclear. This article reports on a case control study of 2,316 HCV seropositive blood donors and 2,316 seronegative donors matched on age, sex, race or ethnicity, blood center, and first time versus repeat donor status. Questionnaires were returned by 758 (33 percent) of the HCV positive subjects and 1,039 (45 percent) of the control subjects. The final multivariate model included only the following independent HCV risk factors: IDU, blood transfusion in non IDU, sex with an injection drug user, having been in jail more than 3 days, religious scarification, having been stuck or cut with a bloody object, pierced ears or body parts, and immunoglobulin injection. Although drug inhalation and a high number of lifetime sex partners were significantly more common among HCV seopositives, they were not associated with HCV after controlling for IDU and other risk factors. The authors conclude that, among United States blood donors, IDU, blood transfusion among non IDU, and sex with an injection drug user are strong risk factors for HCV. Weaker associations must be interpreted with caution. 1 figure. 3 tables. 40 references.

- **Low Incidence of Hepatitis C Virus Transmission Between Spouses: A Prospective Study**

  Source: Journal of Gastroenterology and Hepatology. 15(4): 391-395. April 2000.

  Contact: Available from Blackwell Science. 54 University Street, Carlton South 3053, Victoria, Australia. +61393470300. Fax +61393475001. E-mail: Rob.Turner@blacksci-asia.com.au. Website: www.blackwell-science.com.

  Summary: Interspousal transmission of **hepatitis C virus** (HCV) has been documented; however, the annual risk of interspousal transmission remains unclear. This article reports on a long term prospective study undertaken to define the risk of interspousal transmission of HCV. The index patients (n = 112) with chronic hepatitis C and their anti-HCV seronegative spouses were enrolled. The mean followup period was 45.9 months. Antibodies were tested for in each seronegative spouse every year. Seroconversion of anti HCV occurred in only one spouse, 2 years after enrollment, with a concomitant acute hepatitis. This subject and his spouse were infected with HCV genotype 1b. Nucleotide sequence comparison of the hypervariable region of their HCV genomes showed a homology of 98 percent. Further phylogenetic analysis suggested that they had virtually the same isolate. Accordingly, the annual risk of interspousal transmission of HCV infection was 0.23 percent per year. The authors conclude that their findings suggest a low incidence of interspousal transmission of HCV; however, the risk may be cumulative and such couples should be educated to avoid HCV infection from their spouses. 1 figure. 20 references.

- **Assessment of Fatigue and Psychologic Disturbances in Patients with Hepatitis C Virus Infection**

  Source: Journal of Clinical Gastroenterology. 32(5): 413-417. May-June 2001.

  Contact: Available from Lippincott Williams and Wilkins, Inc. 12107 Insurance Way, Hagerstown, MD 21740. (800) 638-3030 or (301) 714-2300.

Summary: It is a common clinical impression that fatigue is a frequent, and often debilitating, symptom in patients with chronic **hepatitis C virus** (HCV) infection. However, despite its obvious clinical importance, several aspects of fatigue, including its relationship with the underlying liver disease and the presence of psychological disturbances, have not been well examined. This article reports on a study carried out to assess these issues. The subjects (n = 149) were assigned to one of the following study groups: healthy controls (n = 31), chronic HCV infection (n = 24), combined HCV infection and chronic alcohol abuse (n = 32), alcoholic liver disease (n = 22), and chronic non liver diseases (n = 40). All subjects were administered investigator assisted questionnaires designed to analyze the presence of severity of fatigue and psychological abnormalities. The means fatigue scores in patients with chronic HCV infection, alcoholic liver disease, mixed liver disease, and chronic non liver diseases were significantly greater compared to healthy subjects. The total fatigue scores were higher in HCV infected subjects compared with the other patient groups, but the differences failed to reach statistical significance. Moreover, the fatigue experienced by patients with HCV did not improve with rest as effectively as in the other study groups. All patient groups had higher scores for psychological disturbances compared with health subjects. Patients with HCV infection were shown to be more depressed and harbor greater feelings of anger and hostility compared with those with non liver chronic diseases. The authors conclude that these observations are important because proper management of the psychological symptoms may have a favorable impact on the quality of life of patients with HCV infection. 3 tables. 30 references.

- **Combination of Interferon-Alpha and Ribavirin Therapy for Recurrent Hepatitis C Virus Infection After Liver Transplantation**

  Source: Transplantation Proceedings. 32(4): 714-716. June 2000.

  Contact: Available from Appleton and Lange. P.O. Box 86, Congers, NY 10920-0086. (203) 406-4623.

  Summary: Liver transplantation (LT) used as treatment for **hepatitis C virus** (HCV) infection is almost universally associated with a recurrence of infection. More than 60 percent of patients show clinical and histological signs of hepatitis within 1 year of transplantation, and in several studies a rapid development of fibrosis and cirrhosis was reported. This study was undertaken to examine the efficacy, safety, and tolerability of the combination of interferon (IFN) and ribavirin for recurrent HCV infection after LT. Five patients (3 men and 2 women, age range 43 to 63 years) were included in the study; the median time between LT and initiation of treatment was 20 months (range, 10 to 24 months). Only one patient completed the 6 months of combination therapy. He had a normal serum ALT level at the end of the course, but remained serum positive for HCV, and 3 months after completing therapy, his serum ALT increased again. In the other four patients, therapy was discontinued after 1 to 3 months. All four had severe symptomatic hemolysis (breakdown of red blood cells); two patients required blood transfusions. Decreasing the ribavirin dose did not yield an increase in serum hemoglobin level, and ribavirin had to be withdrawn in all 4 patients. No episodes of rejection were recorded. All patients retained stable graft function 3 to 5 years after transplantation. The authors conclude that, despite the small sample size, the study suggests that the combination therapy with IFN and ribavirin after LT for recurrent HCV infection is associated with a high rate of severe side effects necessitating withdrawal of therapy. 1 table. 9 references.

- **Maternal-Infant Transmission of Hepatitis C Virus Infection**

  Source: Hepatology. 36(5 Supplemental 1): S106-S114. November 2002.

  Contact: Available from W.B. Saunders Company. 6277 Sea Harbor Drive, Orlando, FL 19106-3399. (800) 654-2452 or (407) 345-4000.

  Summary: Mother-to-infant transmission of **hepatitis C virus** (HCV) is comparatively uncommon. This article considers the role of mother to infant transmission of HCV infection, including issue relating to pregnancy itself. The prevalence of antibody to HCV (anti-HCV) in pregnancy women is 0.1 percent to 2.4 percent, although in some endemic areas it is much higher. The proportion of women with anti-HCV who have active infection with viremia (virus in the blood) is 60 to 70 percent. Transmission of HCV occurs only when HCV RNA is detectable and may be related to higher levels. The rate of mother-to-infant transmission is 4 to 7 percent per pregnancy in women with HCV viremia. Co-infection with HIV (human immunodeficiency virus) increases the rate of transmission 4 to 5 fold. The actual time and mode of transmission are not known. Elective Cesarean section is not recommended for women with chronic HCV infection alone. The role of treatment to prevent transmission is limited by the fetal toxicity of currently available medications for hepatitis C. Breast feeding poses no important risk of HCV transmission if nipples are not traumatized and maternal hepatitis C is quiescent. Pregnancy women at high risk for HCV infection should be screened for anti-HCV and HCV RNA testing should be performed if anti-HCV is positive. Infants of women with hepatitis C should be tested for HCV RNA on two occasions, between the ages of 2 and 6 months, and again at 18 to 24 months, along with serum anti-HCV. The natural history of mother-to-infant hepatitis C remains uncertain, especially the course in the first year of life when some infants appear to have spontaneous resolution. 3 tables. 71 references.

- **Hepatitis C Virus**

  Source: European Journal of Gastroenterology and Hepatology. 3(8): 572-579. August 1991.

  Summary: The **hepatitis C virus** (HCV) is the recently recognized causative agent of the majority of parentally acquired cases of non-A, non-B (NANB) hepatitis. This article, from a series of six articles that present the current state of the art on type C hepatitis, covers an introduction and history of the discovery of HCV, taxonomic considerations, the genome of HCV, gene products of HCV, antigenic structure, and clinical/virologic correlates. The author concludes that the present knowledge of HCV is still rudimentary. Through the use of the tools of molecular biology, however, the approximate size and sequence of its genome and some information about its translation products are known. 44 annotated references.

- **Limited Humoral Immunity in Hepatitis C Virus Infection**

  Source: Gastroenterology. 116(1): 135-143. January 1999.

  Contact: Available from W.B. Saunders Company. 6277 Sea Harbor Drive, Orlando, FL 19106-3399. (800) 654-2452 or (407) 345-4000.

  Summary: The extremely high rate of chronicity to **hepatitis C virus** (HCV) infection (nearly 80 percent of HCV infections result in persistent infection) suggests an inefficient immune response. This article reports on a study in which the humoral immune response to HCV was evaluated in 60 patients with chronic HCV infection and in 12 patients acutely infected with HCV. A number of recombinant HCV antigens were used

in enzyme linked immunoassays used to evaluated the immune responses of these patients. Immunoglobulin (Ig) G antibody responses to these viral antigens, except for the HCV core, were highly restricted to the IgG1 isotype. Furthermore, antibody responses to HCV viral antigens were of relatively low titer and, with the exception of anti HCV core, were delayed in appearance until the chronic phase of infection. The authors conclude that the IgG1 restriction, low titer, and delayed appearance of antibody responses elicited during HCV infection suggest that the immunogenicity of HCV proteins is limited in the context of natural infection. The authors suggest that the defective humoral immune responses during HCV infection may be attributable to an 'immune avoidance' strategy. 4 figures. 58 references.

- **Preventing Hepatitis B and Hepatitis C Virus Infections in End-Stage Renal Disease Patients: Back to Basics (editorial)**

  Source: Hepatology. 29(1): 291-293. January 1999.

  Contact: Available from W.B. Saunders Company. 6277 Sea Harbor Drive, Orlando, FL 19106-3399. (800) 654-2452 or (407) 345-4000.

  Summary: The impact of hepatitis B (HBV) and C (HCV) on patient survival after kidney transplantation is controversial. This article comments on a study published in the journal that assessed the independent prognostic values of HBsAg and anti-HCV in a large renal transplant population. At 10 years, among all patients with HCV screening (n = 834), 4 variables had independent prognostic values in patient survival: age at transplantation, year of transplantation, biopsy proven cirrhosis, and presence of HCV antibodies. The authors of the commentary note that the findings of the study underscore the importance of preventing hepatitis B and C virus infections in end stage renal disease (ESRD). Patients with ESRD on chronic hemodialysis are at risk for both HBV and HCV infection, despite the success of longstanding infection control practices in the dialysis setting. The authors consider the reasons why infection control strategies are no longer universally implemented and discuss routine hemodialysis unit precautions that could prevent transmission of HBV if the precautions are routinely and rigorously followed. The transmission of HCV infection among chronic hemodialysis patients also might be related to failure to follow routine hemodialysis unit precautions. The authors conclude by reiterating that those responsible for the care of chronic hemodialysis patients should reacquaint themselves with the recommendations for preventing bloodborne pathogen transmission in this setting and ensure that they are performed. 17 references.

- **Hepatitis C Virus in Blood and Dialysate in Hemodialysis**

  Source: American Journal of Kidney Diseases. 37(1): 38-42. January 2001.

  Contact: Available from W.B. Saunders Company. Periodicals Department, 6277 Sea Harbor Drive, Orlando, FL 32887-4800. (800) 654-2452 or (407) 345-4000.

  Summary: The prevalence of **hepatitis C virus** (HCV) positivity among hemodialysis patients remains high compared with that of the healthy population, and thus the issue of safety and environmental protection must be addressed. This article reports on a study undertaken to evaluate the dynamics of prehemodialysis and posthemodialysis blood HCV levels and HCV escape to spent dialysate (and thus to the environment). A serine protease inhibitor (nafamostat mesilate) was used as the anticoagulant for hemodialysis. High flux polysulfone membrane dialyzers were used; dialyzer reuse was not performed. A portion of total spent dialysate (the fluid used for dialysis) was continuously extracted to measure for HCV. No HCV extravasation to spent dialysis

was found, although HCV copy numbers were reduced to a statistically significant level in postdialysis blood compared with predialysis levels. The need to establish standards for risk management in dialysis centers is evident. The data obtained in this study strongly suggest that to minimize the risk for HCV transmission, lower transmembrane pressure (TMP) should be used in the hemodialysis of HCV positive patients, with fresh polysulfone dialyzers and dialysis settings of 180 to 250 milliliters per minute for blood flow, 500 milliliters per minute for dialysate flow, and less than 1.872 mm Hg for TMP. 1 figure. 23 references.

- **Recommendations for Prevention and Control of Hepatitis C Virus (HCV) Infection and HCV-Related Chronic Disease**

  Source: MMWR. Recommendations and Reports. 47(RR-19): 1-39. October 16, 1998.

  Contact: Available from Superintendent of Documents. United States Government Printing Office, Washington, DC 20402. (202) 512-1800. Also available for free at www.cdc.gov or from the Center for Disease Control and Prevention's file transfer protocol server at ftp.cdc.gov.

  Summary: These recommendations expand on previous (1991) recommendations by the Centers for Disease Control (CDC) for preventing **hepatitis C virus** (HCV) infection; these earlier guidelines focused on screening and followup of blood, plasma, organ, tissue, and semen donors. The recommendations in this report provide broader guidelines for preventing transmission; identifying, counseling, and testing persons at risk for HCV infection; and providing appropriate medical evaluation and management of HCV infected persons. The background section covers epidemiology, screening and diagnostic tests, clinical features and natural history, clinical management and treatment, and postexposure prophylaxis and followup. The section on primary prevention recommendations covers blood, plasma derivatives, organs, tissues, and semen; high risk drug and sexual practices; and percutaneous exposures to blood in health care and other settings. The secondary prevention recommendations discuss persons for whom routine HCV testing is and is not recommended, testing for HCV infection, and prevention messages and medical evaluation. The section on public health surveillance covers surveillance for acute HCV, laboratory reports of anti-HCV-positive tests, serologic surveys, and surveillance for chronic liver disease. This report is intended to serve as a resource for health care professionals, public health officials, and organizations involved in the development, delivery, and evaluation of prevention and clinical services. The document includes a posttest and response form readers can use to qualify for continuing medical education credit. 3 figures. 9 tables. 158 references. (AA-M).

- **Clinical Features of Hepatitis C Virus (HCV) Infection in Pregnancy**

  Source: International Journal of Gynecology and Obstetrics. 58(2): 245-246. August 1997.

  Contact: Available from Elsevier Science. P.O. Box 945, New York, NY 10159-0945. (888) 437-4636 or (212) 633-3730. E-mail: usinfo-f@elsevier.com.

  Summary: This article briefly reports on a study that evaluated the incidence of **hepatitis C virus** (HCV) infection, its development, and the role of pregnancy in its evolution in 141 anti-HCV-positive pregnant women. Risk factors were present in 77 subjects (54.6 percent) and absent in 64 (45.4 percent). Clinical evaluations were performed at the beginning of the study, then at 24 to 26 weeks of gestation, at delivery, and 6 months after delivery. Newborns underwent a clinical evaluation to check for HCV infection. In most of the subjects (56.7 percent) HCV positivity was found for the

first time during pregnancy or at delivery. Acute hepatitis was reported by only a small number of patients (11.3 percent). This result underscores the importance of screening for HCV positivity in every pregnancy. HCV-RNA positivity was found in 5 out of 56 newborns checked (8.9 percent). The authors note that the literature reports that HIV infection seems to increase the possibility of HCV transmission between mother and newborn (vertical transmission). However, in this study, the 5 infected babies had HIV negative mothers, which confirms the possibility of vertical transmission of HCV in low-risk populations as well. 1 table. 4 references.

- **Detection of Hepatitis C Virus-Specific Antigens in Semen from Non-A, Non-B Hepatitis Patients**

  Source: Digestive Diseases and Sciences. 37(5): 641-644. May 1992.

  Summary: This article reports on a study in which semen samples from nine patients clinically diagnosed as having non-A, non-B hepatitis (NANBH) were tested by an ELISA using antibodies raised in rabbits against **hepatitis C virus** (HCV)-specific antigens. The semen from all nine patients had elevated levels of HCV-specific antigen in comparison to semen from five healthy donors. Eight of these nine patients had serum reactive for HCV-specific antibodies in the ELISA using HCV-specific antigens. This more direct evidence for viral presence supports the earlier epidemiological data suggesting that HCV could be transmitted sexually. 3 tables. 18 references. (AA-M).

- **Chronic Hepatitis C Virus Infection Causes a Significant Reduction in Quality of Life in the Absence of Cirrhosis**

  Source: Hepatology. 27(1): 209-212. January 1998.

  Contact: Available from W.B. Saunders Company. 6277 Sea Harbor Drive, Orlando, FL 19106-3399. (800) 654-2452 or (407) 345-4000.

  Summary: This article reports on a study that assessed the effects of chronic **hepatitis C virus** (HCV) infection, in the absence of cirrhosis (liver scarring), on patients quality of life (QOL). Assessment was done by using the short form 36 (SF36) symptomatology questionnaire. Patients with chronic hepatitis C were polysymptomatic (had many symptoms) and had significant reductions in their SF36 scores for all of the modalities tested. By contrast, patients with chronic hepatitis B virus (HBV) infection showed a reduction in the SF36 scores that assessed mental function, but no decrease in the scores that measured physical symptoms, indicating that the symptoms associated with chronic HCV infection are qualitatively different from those associated with chronic HBV. Patients with chronic HCV infection who had used intravenous drugs in the past had the greatest impairment in QOL scores, but the reduction was found even in patients who had never used drugs. The reduction in QOL could not be attributed to the degree of liver inflammation or to the way the infection was acquired. The authors conclude that chronic infection with HCV per se gives rise to physical symptoms that reduce the QOL of those who have it. 2 figures. 1 table. 13 references. (AA-M).

- **Hepatitis C Virus Infection in a Community in the Nile Delta: Risk Factors for Seropositivity**

  Source: Hepatology. 33(1): 248-253. January 2001.

  Contact: Available from W.B. Saunders Company. 6277 Sea Harbor Drive, Orlando, FL 19106-3399. (800) 654-2452 or (407) 345-4000.

Summary: This article reports on a study undertaken to identify risk factors for **hepatitis C virus** (HCV) infection in a rural village in the Nile Delta with a high prevalence of antibodies to HCV (anti HCV). One half of the village households were systematically selected, tested for anti HCV, and interviewed. Of this group (n = 3999), 973 (24.3 percent) were anti HCV positive, reflecting prior HCV infection but not necessarily current liver disease, with nearly equal prevalence among males and females. Anti HCV prevalence increased sharply with age among both males and females, from 9.3 percent in those 20 years of age and younger to greater than 50 percent in those older than 35 years of age. Among those over 20 years of age, the following risk factors were significantly associated with seropositivity: age, male gender, marriage, anti schistosomiasis injection treatment, blood transfusion, invasive medical procedure (surgery, catheterization, endoscopy, or dialysis), receipt of injections from 'informal' health care provider, and cesarean section or abortion. Exposures not significantly related to anti HCV positivity in adults included history of, or active infection with, Schistosoma mansoni; sutures or abscess drainage; goza smoking in a group; and shaving by community barbers. Among those 20 years old or younger, no risk factors were clearly associated with anti HCV positivity; however, circumcision for boys by informal health care providers was marginally associated with anti HCV. The authors note that prevention programs focused primarily on culturally influenced risks in rural Egyptian communities are being implemented and evaluated. 7 tables. 32 references.

- **Approach to the Patient with Chronic Hepatitis C Virus Infection**

  Source: Annals of Internal Medicine. 136(10): 747-757. May 21, 2002.

  Contact: Available from American College of Physicians. American Society of Internal Medicine. 190 North Independence Mall West, Philadelphia, PA 19106-1572. Website: www.acponline.org.

  Summary: This article reviews the approach to a patient with chronic **hepatitis C virus** (HCV) infection, a common and often asymptomatic disease. Antibodies against HCV are a highly sensitive marker of infection. Molecular testing for HCV is used to confirm a positive result on antibody testing and to provide prognostic information for treatment; however, quantitative HCV RNA does not correlate with disease severity or risk for progression. Chronic HCV infection is most frequently associated with remote or current intravenous drug use and blood transfusion before 1992, although as many as 20 percent of infected patients have no identifiable risk factor. In an estimated 15 to 20 percent of persons infected with HCV, the infection progresses to cirrhosis (liver scarring); alcohol intake is an important cofactor in this progression. Most specialists prefer to include an examination of liver histology (by biopsy) in the management of patients with chronic HCV infection to aid prognostic and treatment decision. The current standard of drug therapy for chronic HCV is weekly subcutaneous peginterferon in combination with daily oral ribavirin, which results in sustained virologic response in approximately 55 percent of chronically infected patients. Side effects of interferon therapy include myalgias, fever, nausea, irritability, and depression. The cost-effectiveness of interferon therapy is similar to that of many commonly accepted medical interventions. The author concludes that the primary care physician serves a vital role in identifying patients with chronic HCV infection, educating patients about risk factors for transmission, advising patients about the avoidance of alcohol, and aiding patients in making treatment decisions. 4 tables. 100 references.

- **Screening for Hepatitis C Virus Infection: Recommendation from the U.S. Preventive Services Task Force**

  Source: Annals of Internal Medicine. 140(6): I-62. March 2004.

  Summary: This article summarizes for patients and lay readers the U.S. Preventive Services Task Force (USPSTF) recommendations on screening for **hepatitis C virus** (HCV) infection. These recommendations are based on the USPSTF's examination of evidence specific to asymptomatic persons for HCV testing and treatment. The complete information on which this summary is based, including evidence tables and references, is available in the accompanying article in this same issue, and in the summary of the evidence and systematic evidence review on this topic. These materials are also available on the USPSTF web site (www.preventiveservices.ahrq.gov). The USPSTF recommends against routine screening for HCV infection in asymptomatic adults who are not at increased risk (general population) for infection. The prevalence of HCV infection in the general population is low, and most who are infected do not develop cirrhosis (liver scarring) or other major negative health outcomes. There is no evidence that screening for HCV infection leads to improved long term health outcomes, such as decreased cirrhosis, hepatocellular cancer, or mortality. The current treatment regimen is long and costly and is associated with a high patient dropout rate due to adverse effects.

- **Screening for Hepatitis C Virus Infection in Adults: Recommendation Statement**

  Source: Annals of Internal Medicine. 140(6): 462-464. March 2004.

  Summary: This article summarizes the U.S. Preventive Services Task Force (USPSTF) recommendations on screening for **hepatitis C virus** (HCV) infection. These recommendations are based on the USPSTF's examination of evidence specific to asymptomatic persons for HCV testing and treatment. The complete information on which this summary is based, including evidence tables and references, is available in the accompanying article in this same issue, and in the summary of the evidence and systematic evidence review on this topic. These materials are also available on the USPSTF web site (www.preventiveservices.ahrq.gov). The USPSTF recommends against routine screening for HCV infection in asymptomatic adults who are not at increased risk (general population) for infection. The prevalence of HCV infection in the general population is low, and most who are infected do not develop cirrhosis (liver scarring) or other major negative health outcomes. There is no evidence that screening for HCV infection leads to improved long term health outcomes, such as decreased cirrhosis, hepatocellular cancer, or mortality. The current treatment regimen is long and costly and is associated with a high patient dropout rate due to adverse effects. 3 references.

- **Confirming the Diagnosis of Hepatitis C Virus Infection**

  Source: Journal of Critical Illness. 15(7): 350. July 2000.

  Contact: Available from Cliggott Publishing Company. 55 Holly Hill Lane, Greenwich, CT 06831-0010. (203) 661-0600.

  Summary: This brief article reviews the strategies undertaken to confirm the diagnosis of **hepatitis C virus** (HCV) infection. The first line test for diagnosing HCV infection is the HCV antibody test, an enzyme linked immunosorbent assay that is easy to perform, cost effective, and highly sensitive for detecting HCV infection in a patient who is not immunocompromised. Currently, the second generation anti HCV test is used by most institutions; a third generation assay with improved sensitivity has been approved but is

not yet widely used. In general, patients should undergo HCV antibody testing if they admit to any of the risk factors for hepatitis C or if they have elevated liver enzyme levels, regardless of the degree of elevation. When a positive test result is obtained in a patient with risk factors for hepatitis C and elevated liver enzyme levels, the diagnosis of hepatitis C is more than 95 percent certain. To confirm ongoing viremia (virus status in the blood), testing for HCV RNA by polymerase chain reaction (PCR) is recommended. PCR testing is not recommended for first line testing because it is expensive, difficult to perform, and can yield both false positive and false negative results. One chart lists the indications (risk factors) for testing for **hepatitis C virus.** 1 table. 1 reference.

- **Chronic Hepatitis C Virus Infection-A Disease in Waiting? (editorial)**

  Source: New England Journal of Medicine. 327(27): 1949-1950. December 31, 1992.

  Summary: This brief article, serving as an introduction to two other studies reported in this journal, discusses chronic **hepatitis C virus** (HCV) infection. Topics include the discovery of HCV (previously referred to as non-A, non-B hepatitis); the long-term nature of HCV and the concomitant requirement for long-term follow-up care; community-acquired HCV infection; the consequences of unresolved HCV infection; and treatment programs, including the use of recombinant interferon. The author concludes that recent observations heighten the awareness of the disease potential of HCV infection and provide a realistic hope that dire consequences are unusual. 9 references.

- **Hepatitis C Virus Infection and Needle Exchange Use Among Young Injection Drug Users in San Francisco**

  Source: Hepatology. 34(1): 180-187. July 2001.

  Contact: Available from W.B. Saunders Company. 6277 Sea Harbor Drive, Orlando, FL 19106-3399. (800) 654-2452 or (407) 345-4000.

  Summary: Young injection drug users (IDUs) in San Francisco may be at high risk for **hepatitis C virus** (HCV) infection, despite access to several needle exchange venues. This article reports on a cross sectional study conducted from 1997 to 1999 in San Francisco to estimate the prevalence and incidence of antibody to HCV (anti HCV) among street recruited IDUs under age 30, and to examine risk behaviors and sources of sterile needles. Among 308 participants, the prevalence of anti HCV was 45 percent. Using statistical modeling, incidence of HCV infection was estimated to be 11 per 100 person years. Independent risk factors for anti HCV included age, years injecting, years in San Francisco, first injected by a sex partner, injected daily, ever borrowed a needle, bleached last time a needle was borrowed, snorted or smoked drugs in the prior year, and injected by someone else in the prior month. In the prior month, 88 percent of the study used at least 1 of several needle exchange venues, and 32 percent borrowed a needle. The authors conclude that anti HCV prevalence is lower than in previous studies of older IDUs, but 11 percent incidence implies high risk of HCV infection in a long injecting career. Despite access to sterile needles, borrowing of needles persisted. 1 figure. 5 tables. 60 references.

Federally Funded Research on Hepatitis C Virus

The U.S. Government supports a variety of research studies relating to hepatitis C virus. These studies are tracked by the Office of Extramural Research at the National Institutes of Health.[2] CRISP (Computerized Retrieval of Information on Scientific Projects) is a searchable database of federally funded biomedical research projects conducted at universities, hospitals, and other institutions.

Search the CRISP Web site at **http://crisp.cit.nih.gov/crisp/crisp_query.generate_screen**. You will have the option to perform targeted searches by various criteria, including geography, date, and topics related to hepatitis C virus.

For most of the studies, the agencies reporting into CRISP provide summaries or abstracts. As opposed to clinical trial research using patients, many federally funded studies use animals or simulated models to explore hepatitis C virus. The following is typical of the type of information found when searching the CRISP database for hepatitis C virus:

- **Project Title: A CELL-BASED ASSAY TO MEASURE HCV DRUG SUSCEPTIBILITY**

  Principal Investigator & Institution: Parkin, Neil T.; Virologic, Inc. South San Francisco, Ca 94080

  Timing: Fiscal Year 2003; Project Start 01-SEP-2003; Project End 31-AUG-2005

  Summary: (provided by investigator): Chronic infection with **hepatitis C virus** (HCV) is an important cause of life-threatening liver disease worldwide. Current treatments for HCV are poorly tolerable and incompletely effective, especially for HCV of certain subtypes (1a and 1b) that are prevalent in North America, Europe and Japan. Thus there are many pharmaceutical companies which are developing novel anti-HCV drugs. However, based on experience with other chronic viral infections such as HIV-1, antiviral drug resistance will likely be an important cause of failure of antiviral chemotherapy. Thus we anticipate the need for assays to measure susceptibility of patient-derived HCV to antiviral drugs. The goal of this project is to develop a rapid (<14 day), sensitive HCV drug susceptibility assay. The proposed assay will be performed using recombinant HCV replicons that contain a reporter gene (e.g. luciferase). A segment of each HCV replicon is derived from patient isolates and encodes a specific antiviral drug target (e.g. HCV protease/ helicase or polymerase). Permissive hepatic cell cultures are transfected with HCV replicon RNA and drug susceptibility/resistance is evaluated by comparing reporter gene expression levels in the presence and absence of antiviral drugs. The principal applications for the proposed assay are as follows. First, it can be used to aid in the discovery and development of first generation anti-HCV drugs by characterizing resistance in vitro. Second, it will be an important tool for monitoring the development of drug resistant HCV during the clinical evaluation of investigational anti-HCV agents. Third, it can be used to select optimal drug combinations for patients considering, undergoing, or failing anti-HCV drug therapy. Finally, it can be used to aid the discovery and development of second-generation drugs that are active against drug resistant strains, by screening new drug candidates against HCV replicon vector libraries. As a result of the first two potential applications, it is advantageous to develop the proposed assay before there is a

[2] Healthcare projects are funded by the National Institutes of Health (NIH), Substance Abuse and Mental Health Services (SAMHSA), Health Resources and Services Administration (HRSA), Food and Drug Administration (FDA), Centers for Disease Control and Prevention (CDCP), Agency for Healthcare Research and Quality (AHRQ), and Office of Assistant Secretary of Health (OASH).

perceived clinical need for it, which would result from the development of resistance following use of specific anti-HCV drugs in patients.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: A NOVEL APPROACH TO STUDY HEPATITIS C VIRUS ENTRY**

  Principal Investigator & Institution: Singh, Ila R.; Pathology; Columbia University Health Sciences Po Box 49 New York, Ny 10032

  Timing: Fiscal Year 2002; Project Start 01-SEP-2002; Project End 31-AUG-2004

  Summary: (provided by applicant): **Hepatitis C virus** infects 4 million Americans and an estimated 2-4% of the world's population, causing chronic hepatitis in most of those infected. A sizable fraction subsequently develops cirrhosis or hepatocellular carcinoma. This proposal describes the use of a novel approach to perform a mutational analysis of regions of the **Hepatitis C virus** (HCV). The objective is to delineate, at an unprecedented resolution, the role of specific sequences, both viral and cellular, in viral entry. Conventional approaches to the study of viral entry consist of morphological and biochemical studies of replication intermediates. While these approaches have been very useful for many viruses, they suffer from some drawbacks. Since viral entry is an inefficient process, with only one out of hundreds or thousands of virions following the productive pathway of infection, the non-productive particles tend to severely obscure morphological analysis and limit interpretation of biochemical studies. It also becomes difficult to get an adequate signal with physiologically relevant multiplicities of infection. This is especially pertinent to the study of the early steps of viral infection, before there is any amplification from viral expression. These problems make it necessary to complement conventional studies with the genetic approach of making and analyzing mutations that disrupt viral functions. The mutational approach is a proven and well-established strategy for the study of gene function. However, most current methods involve the isolation, storage and characterization of each mutant separately, making the process very time consuming and labor intensive. Genetic footprinting is a novel method that allows for efficient construction and parallel functional analysis of thousands of mutations in a cloned gene. The specific aims of this research are: 1) Creation of libraries of mutations in the E1 and E2 envelope glycoproteins of HCV, using a transposon-based mutagenesis method, followed by their analysis. 2) Genetic footprinting of the HCV IRES, to determine regions necessary for its function. Preliminary data showing the successful generation of libraries is presented. These libraries will be analyzed en masse to determine what regions of the glycoproteins are necessary for viral binding and fusion, and to determine what regions of the IRES are essential for translation of viral proteins. A comprehensive and detailed knowledge of the process of HCV entry gained from this study will be important for understanding the mechanism of viral infection and for the development of new preventive and therapeutic approaches against HCV.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: ACUTE HEPATITIS C INFECTION FOLLOWING CD8 DEPLETION**

  Principal Investigator & Institution: Cawthon, Andrew G.; Children's Research Institute 700 Children's Dr Columbus, Oh 432052664

  Timing: Fiscal Year 2003; Project Start 01-AUG-2003; Project End 31-JUL-2006

  Summary: (provided by the applicant): The **hepatitis C virus** (HCV) infects approximately 2% of the global population. The majority (70%) of individuals exposed to the virus develop a persistent, life-long infection that over a period of years can result

in cirrhosis of the liver or even hepatocellular carcinoma. It is thought that T cell mediated immune responses are important for spontaneous resolution of infection but the relative contribution of CD4+ and CD8+ subsets are not known. In order to directly address the role of CD8+ T cells during acute HCV infection, chimpanzees will be temporarily depleted of CD8+ T cells prior to challenge with HCV. This experimental approach will address the following aims: 1) To assess how HCV replication and liver pathology is altered by depletion of CD8+ T cells prior to infection, 2) To study the evolution of the CD4+ T cell response to acute HCV infection during the absence and recovery of the CD8+ T cell compartment, and 3) To determine if eliminating the selective pressure mediated by CDS+ T cells alters the evolution of class I and class II MHC restricted HCV epitopes. Results from the experiments proposed in this research plan should contribute to our understanding of HCV pathogenesis by providing a detailed temporal analysis of the kinetics of viral replication and liver pathology during the absence and recovery of the CDS+ T cell compartment following HCV infection. These studies will also provide important new information as to the relative importance of CD8+ and CD4+ T cell responses in the control of HCV infection while determining if a correlation exists between the emergence of antigen specific T cells, the evolution of escape mutations, and the kinetics of virus replication in vivo.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: ADULT AIDS CLINICAL TRIALS UNIT**

  Principal Investigator & Institution: Balfour, Henry H.; Professor of Laboratory Medicine, Pathol; Lab Medicine and Pathology; University of Minnesota Twin Cities 200 Oak Street Se Minneapolis, Mn 554552070

  Timing: Fiscal Year 2002; Project Start 01-MAR-1992; Project End 31-DEC-2004

  Summary: (adapted from the application's abstract): The Minnesota AIDS Clinical Trials Unit (ACTU) requests to continue to be a unit of the Adult AIDS Clinical Trials Group (AACTG). The Minnesota ACTU is committed to the Scientific Agenda of the AACTG, in which they have participated continuously since January 1, 1987. In addition to recruiting and retaining a cohort of new HIV-infected patients in clinical trials (estimated to be 85 patients in main studies and 54 patients in substudies annually), the Minnesota ACTU plans to contribute to the Group Scientific agenda with the following specific aims: (1) to correlate the quantity and replication competence of HIV at the cellular level in lymphoid tissue (LT), peripheral blood fractions and other compartments; (2) to develop more sensitive methods to detect HIV and apply these to selection of more effective therapies; (3) to define the natural history of cytomegalovirus (CMV) disease in the era of potent antiretroviral therapy and determine the best assays (virologic and immunologic) to monitor its clinical course (AACTG 360); (4) to identify and properly manage the patients who are at risk for complications of the dyslipidemias associated with potent antiretroviral therapy; (5) to identify resistant CMV strains and assess their pathogenicity; (6) to study relationships between the production of neurotoxins in plasma and cerebrospinal fluid of HIV-infected patients, neuronal loss as measured by proton magnetic resonance spectroscopy and the development or progression of HIV-associated dementia (HAD); and (7) to understand and characterize pharmacokinetic behavior, including drug-drug interactions, of antiretrovirals and other HIV-related drugs in biologic fluids. To help achieve these specific aims, the Minnesota ACTU has both Virology and Pharmacology Advanced Technology Laboratories (ATL). The Virology ATL is focusing on quantitation and characterization of HIV in lymphoid tissue and other body compartments. This laboratory also has expertise in HIV and CMV resistance. The Pharmacology ATL is developing assays for simultaneous

determination of levels of protease inhibitors and measurement of intracellular antiretroviral anabolites. The Nebraska subunit has a special interest in neuroAIDS and has identified neurotoxins putatively responsible for pathology in HAD. The Iowa subunit has expertise in the detection of hepatitis C and will be collaborating in studies of the pathogenesis of coinfection with HIV and hepatitis C.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: ADULT AIDS CLINICAL TRIALS UNIT**

  Principal Investigator & Institution: Goldman, Mitchell; Medicine; Indiana Univ-Purdue Univ at Indianapolis 620 Union Drive, Room 618 Indianapolis, in 462025167

  Timing: Fiscal Year 2002; Project Start 01-JAN-2000; Project End 31-DEC-2004

  Summary: (adapted from application's abstract): The Indiana University proposes to build upon the following in the renewal application: (1) scientific and administrative contributions. The Indiana ACTU ranks among the top 20 percent of ACTUs scientifically; (2) cost efficient accrual into AACTG trials. Indiana ranked third in cost weighed accrual; and (3) recruitment of women and minorities. The ACTU ranked second in recruitment of African- Americans and third in women. The long-term objectives of this site are to: expand scientific and administrative contributions through recruitment of additional investigators; increase accrual potential for women and minorities by expansion of the Wishard Hospital subunit; and increase the patient base by establishing a subunit at Community Hospital of Indianapolis. The first specific aim of the Indiana University ACTU is to contribute scientifically through submission of concept proposals and memberships on AACTG protocol teams and committees. Currently, Indiana investigators hold 32 positions on protocol teams. Concepts are proposed for: (a) salvage therapy for efavirenz failures; (b) evolution of anal dysplasia and the role of HPV in patients on HAART; (c) the role of gp 120 in HIV induced apoptosis of neurological cells in pathogenesis of dementia; (d) the role of GM-CSF and CD4 ligand on immunity to H. Capsulatum and HIV-1; (e) use of in vitro assays for drug interactions with protease inhibitors; and (f) the role of intestinal metabolism and bioavailability of antiretroviral drugs. The second specific aim is to expand the patient base, including women and minorities, though increased support for subunits at Wishard Hospital and Community Hospital. The work proposed in this application will be implemented through conduct of clinical trials as a member the AACTG, using an infrastructure that has been refined during 12 years as an ACTU. Specialized immunology, virology, and pharmacology laboratories will support this work.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: AIDS CLINICAL TRIALS GROUP - ACTU**

  Principal Investigator & Institution: Feinberg, Judith T.; Internal Medicine; University of Cincinnati 2624 Clifton Ave Cincinnati, Oh 45221

  Timing: Fiscal Year 2002; Project Start 30-SEP-1987; Project End 31-DEC-2004

  Summary: (adapted from the applicantion's abstract): Since its inception in 1987, the University of Cincinnati (UC) ACTU has made contributions to the overall mission of the ACTG in a number of key areas. The UC ACTU has provided both scientific and administrative leadership especially in opportunistic infections, and more recently, in antiretroviral studies, HIV- associated neurologic diseases, research nursing, and study design. In the current cycle, the UC ACTU proposes to continue to perform a broad range of clinical trials and substudies to assure maximum UC ACTU contribution to the objectives of the ACTG research agenda. These include to translate the findings of basic

research conducted at UC on immunopathogenesis of Pneumocystis carinii and other opportunistic pathogens that may help determine when and if prophylaxis can be discontinued safely in antiretroviral therapy responders. Also, to explore microbial and immunologic measures which define risk for the protection against Pneumocystis as a basis for adjunctive immune- based therapy and prophylaxis. In addition to study the pathogenesis and clinical significance of hepatitis C/HIV co-infection in the HARRT era, and use this knowledge to develop improved treatments. Another Aim is to continue to elucidate the underlying mechanisms in the neuropathogenesis of HIV infection, and exploit these mechanisms in the development of new therapeutic modalities for central nervous system HIV infection, including HIV dementia and multifocal leukoencephalopathy. The UC ACTU will also work to develop treatment strategies for the management of patients with discordant responses to current antiretroviral therapy and to develop simplified, potent treatment strategies, including the use of novel agents, to enhance antiretroviral adherence and therefore improve clinical outcome. The short and longer-term incremental cost of quality-adjusted life expectancy associated with various treatment strategies using utility assessment will also be studied. Finally, the UC ACTU proposes to evaluate whether an intensive educational intervention that is paced by the patient yields improved short and long-term virologic suppression in naive patients.

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- **Project Title: ALCOHOL EFFECTS ON LIVER DISEASE IN HCV AND HIV COINFECT**

  Principal Investigator & Institution: Schmidt, Warren N.; Assistant Professor; Internal Medicine; University of Iowa Iowa City, Ia 52242

  Timing: Fiscal Year 2002; Project Start 25-SEP-2000; Project End 31-JUL-2004

  Summary: (Applicant's Abstract) Hepatitis C (HCV) and Human Immunodeficiency virus (HIV) cause chronic infections of worldwide importance. Because they share parenteral factors for transmission, over one third of patients with HIV are usually co-infected with HCV and nearly 400,000 individuals in the United States are positive for both viruses. Patients with co-infection have more aggressive liver disease and increased incidence of cirrhosis than patients with HCV only. While the reasons for this are unclear, it is possible that co-existent alcoholism in this population is at least partially responsible. Alcohol may further modulate host immune suppression and have specific effects on host immune defenses resulting in increased viral replication and mutational pressure on HCV. The overall goal of this proposal is to study and clarify the effects of alcohol on HCV and progressive liver disease in patients who are co-infected with HIV. The specific aims are: 1) We will evaluate a cohort of HCV/HIV positive patients and identify the sociodemographic, histological, and clinical variables of these individuals that are affected by excess alcohol consumption and most likely to be important for progressive liver disease. 2) We will then sequence and compare important genomic regions of HCV isolated from these patients and determine the significance of quasispecies diversity for HCV pathology. 3) We will study the effects of antiviral therapy on the composition and diversity of HCV genomic regions and determine their importance for patient prognosis and response to therapy. Our work will clarify the epidemiology, natural history, and pathology of alcohol in these patients. It will also provide an increased understanding of progressive liver disease in this population that will aid in future management and antiviral therapy.

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- **Project Title: AMPLIFICATION OF CUSTOM RNA IN PLANTS**

  Principal Investigator & Institution: Kazakov, Sergei A.; Somagenics, Inc. Santa Cruz, Ca 95060

  Timing: Fiscal Year 2002; Project Start 01-AUG-1998; Project End 31-AUG-2004

  Summary: (provided by applicant): RNA-based technologies have become increasingly prominent in research and biotechnology since the discovery of catalytic RNA (ribozymes), techniques for selection of novel functions from random libraries of RNA, and the widespread use of microarrays. However, the cost of producing RNA by synthetic or enzymatic means remains high-at least ten times the cost of DNA, and synthetic methods are limited to short RNAs. This proposal describes a novel method for the low-cost, largescale production of custom RNA products of any length based on amplification in plants using viral vectors, an approach that has been successfully used for the production of protein products. After infection with recombinant virus, the plants are harvested, virions are isolated using an established, single-step procedure, RNA is extracted, and the desired fragment is excised and purified in a simple procedure. Yields of viral RNA are approximately 0.5 percent of total dry plant mass. In Phase I of this project we established proof of principle by demonstrating the insertion of a custom RNA fragment into the viral RNA vector, which remained completely stable and intact under normal storage and in vivo conditions. Upon addition of a new solution component, the insert was efficiently excised from the vector. In Phase II, we will develop this approach into a practical method ready for commercialization. This will involve a series of optimizations to make the system robust enough to overcome any obstacles that may emerge for certain custom RNAs. Our first demonstration of large-scale RNA production from plants will be to several hundred milligrams of a candidate therapeutic ribozyme and a key element of the **hepatitis C virus.** PROPOSED COMMERCIAL APPLICATION: RNA is an important target for structural biology and biomedical studied including HIV and influenza viruses. It also has potential in antisense and ribozyme therapeutics, biotechnology products and molecular biology tools: Our technology would provide large amounts of custom RNAs less expensively and more efficiently than alternative methods. Our current business strategy is to sell custom RNA in partnership with Large Scale Biology Corp. and license the technology to certain other manufacturers.

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- **Project Title: ANTIVIRAL & ANTIFIBROTIC LIVER THERAPY OF HCV+ DRINKERS**

  Principal Investigator & Institution: Lieber, Charles S.; Professor of Medicine & Pathology; Medicine; Mount Sinai School of Medicine of Nyu of New York University New York, Ny 10029

  Timing: Fiscal Year 2002; Project Start 01-SEP-2000; Project End 31-MAY-2005

  Summary: We plan to evaluate a combined antiviral, antifibrotic and antioxidant treatment in the progression of liver disease of heretofore excluded patients with hepatitis C namely alcohol drinkers. Abstainers or alcohol consumers will be given state- of-the-art antiviral treatment (pegylated interferon + ribavirin) for 24-48 weeks. Another innovative aspect of this proposal is the supplemention with an anti-fibrotic agent, namely polyenylphosphatidylcholine (PPC) extracted from soybeans, or placebo, administered for 3 years (concomitantly with the antiviral treatment and thereafter). Current therapy neglects the fact that what causes the major medical symptoms and eventually the demise of the patient is liver fibrosis, resulting cirrhosis and associated

complications, including hepatocellular carcinoma. If the fibrotic process could be stopped or even prevented, the **hepatitis C virus** would lose much of its impact on health. Available anti-fibrotic agents are too toxic to be used in patients, except for one, namely PPC, which has been shown in various experimental models to have striking anti-fibrotic actions, and which was found recently to be beneficial in HCV+ patients in terms of their circulating levels of transaminases. Fibrosis was not assessed, but documentation of the effects of PPC on fibrosis in HCV+ patients is being proposed here. It is noteworthy that PPC was discovered to have also significant anti- oxidant effects. This may be important in HCV+ patients since various studies have now indicated that HCV is associated with an oxidative stress. Another innovative aspect is the inclusion of drinkers who thus far were excluded from standard antiviral treatment, mainly because of concerns about exacerbation of mental disorders, reliability and compliance. However, the latter objection has now been overcome by the availability of pegylated interferon which can be administered once a week by the therapist in a controlled fashion. For both PPC and ribavirin, compliance will be monitored by incorporation of markers, such as riboflavin, that can be measured in the urine. Spot checks of blood levels of dilinoleoylphosphatidylcholine (DLPC, the main phosphatidylcholine species of PPC) will also be performed. Accordingly, support is requested for a a double-blind, randomized placebo controlled study to assess the efficacy of this novel approach for the treatment of liver disease in HCV+ alcohol consumers or abstainers. Funds are requested for special laboratory tests, study nurses, travel to meetings, patient monitoring expenses and a core office.

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- **Project Title: BACULOVIRUS MEDIATED GENE DELIVERY OF HEPATITIS C VIRUS**

  Principal Investigator & Institution: Isom, Harriet C.; Distinguished Professor; Microbiology and Immunology; Pennsylvania State Univ Hershey Med Ctr 500 University Drive Hershey, Pa 170332390

  Timing: Fiscal Year 2002; Project Start 01-SEP-2000; Project End 31-AUG-2004

  Summary: (Applicant abstract): Chronic **hepatitis C virus** (HCV) infection is associated with the development of cirrhosis, an elevated risk of hepatocellular carcinoma and is currently responsible for almost 30 percent of end-stage liver disease in need of transplantation in the United States. At present, no means of prevention of HCV infection exists and treatments are unsatisfactory. HCV is highly species-specific. Only humans and a few high primates are susceptible. The only animal model for HCV vaccine or antiviral research is the endangered chimpanzee. One of the major reasons that vaccine development and antiviral therapy are lacking for HCV stems from the fact that there are no satisfactory small animal or in vitro model systems for studying HCV replication. The applicant has recently reported a novel in vitro system for delivering a replication competent HBV to cells of hepatic origin by using an HBV recombinant baculovirus. In HBV baculovirus infected HepG2 cells, HBV transcripts, intracellular and secreted HBV antigens are produced and replication occurs as evidenced by the presence of high levels of intracellular replicative intermediates and protected HBV DNA in the medium. Covalently closed circular DNA is present indicating that, in this system, HBV core particles are capable of delivering newly synthesized HBV genomes back into the nucleus of infected cells. She has also demonstrated that the HBV recombinant baculovirus system can be used to monitor the effects of an antiviral on multiple aspects of the HBV life cycle include formation of newly synthesized CCC DNA as well as the effects on preexisting CCC DNA. Based on the success with

generation and usage of the HBV recombinant baculovirus system, she will test in this proposal the following hypothesis: An HCV recombinant baculovirus can be generated which is replication competent in human hepatic cells in culture and can be used to study molecular aspects of HCV replication and effects of specific anitivirals on HCV replication. The Specific Aims are: 1. To generate recombinant baculoviruses that contain all or part of the HCV cDNA under the control of mammalian promoters. 2. To test the ability of HCV-recombinant baculoviruses to express HCV gene products and replicate HCV in human cells of hepatic origin. 3. To use recombinant HCV baculovirus to evaluate the direct effect of interferon treatment on evolution of quasispecies during HCV replication in cells of hepatic origin.

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- **Project Title: CHIMERIC VIRUS PRIMATE MODEL OF HEPATITIS C**

  Principal Investigator & Institution: Lemon, Stanley M.; Professor & Dean, Sch. of Medicine; Microbiology and Immunology; University of Texas Medical Br Galveston 301 University Blvd Galveston, Tx 77555

  Timing: Fiscal Year 2002; Project Start 15-FEB-2002; Project End 31-JAN-2006

  Summary: (Provided by the applicant): Chronic HCV infection is a major threat to the public health. Current therapies have limited efficacy, but the search for more effective treatments is hampered by the lack of available animal models of HCV infection. The chimpanzee (Pan troglodytes) is the only animal species permissive for infection with this virus. This deficiency will be addressed by developing a small nonhuman primate model of hepatitis C involving the closely related, unclassified flavivirus GBV-B. GBV-B replicates to high titers, is hepatotropic, and causes liver disease in susceptible tamarins (Saquinus sp.). Since tamarins are more readily available than chimpanzees for such studies, GBV-B infection of these animals represents a potentially useful surrogate for studies of hepatitis C. However, although GBV-B among all animal viruses has the closest phylogenetic relationship to HCV, its proteins still share only approximately 25% identity at the amino acid level. Moreover, unlike HCV, GBV-B does not appear capable of establishing persistent infection in these animals. These features of GBV- B limit its usefulness. To overcome these limitations, the applicants will construct chimeric genome-length GBV-B cDNA clones in which specific functional domains of HCV are inserted in lieu of homologous GBV-B sequence. The hypothesis is that the close phylogenetic relationship between GBV-B and HCV will allow the rescue of viable chimeric viruses from these clones, and that these viruses will represent uniquely valuable resources to the research community since they will allow the in vivo evaluation of candidate inhibitors of critical HCV replication functions in a readily available and relatively inexpensive small, nonhuman primate species. Under Aim 1, the investigators have constructed a fulllength, infectious cDNA copy of the GBV-B genome. The infectivity of RNA transcribed from this clone has been demonstrated following intrahepatic injection of the RNA in a susceptible tamarin. In Aim 2, the investigators are constructing infectious chimeric flavivirus cDNAs containing the following HCV domains within a GBV-B background: the internal ribosome entry site (IRES), the major proteinase (NS3) with its cofactor molecule (NS4A), the RNA helicase (NS3) and the RNA dependent, RNA polymerase (NSSB). In Aim 3, chimeras in which the structural proteins of GBV-B and HCV are placed within the genetic background of the alternate virus will be constructed. For both Aims 2 and 3, the applicants will assess the ability of RNAs transcribed from these chimeric cDNA clones to induce infection in tamarins following intrahepatic inoculation, and determine the extent to which the

viruses rescued from these clones cause acute or chronic liver disease on subsequent passage in these nonhuman primates.

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- **Project Title: CIS-ACTING RNA ELEMENTS IN HEPATITIS C VIRUS REPLICATION**

  Principal Investigator & Institution: Luo, Guangxiang G.; Associate Professor; Microbiology Immunology, and Molecular Genetics; University of Kentucky 109 Kinkead Hall Lexington, Ky 40506

  Timing: Fiscal Year 2003; Project Start 01-JAN-2003; Project End 31-DEC-2007

  Summary: (provided by applicant): **Hepatitis C virus** (HCV) is the major etiologic agent of non-A, non-B (NANB) viral hepatitis, infecting approximately 4 million people in the U.S. HCV has a positive-stranded RNA genome consisting of a single open reading frame (ORF) flanked by the untranslated regions (UTR) at the 5' and 3' ends. The ORF encodes a large polypeptide that is processed to structural and nonstructural viral proteins. The roles of viral proteins and conserved RNA sequences/structures in HCV replication are poorly understood. The overall goal of this research proposal is to determine the sequence and structural requirements of cis-acting RNA elements in the 5' and 3' UTRs in viral RNA replication. Both the 5' and 3' UTR sequences are highly conserved among various HCV isolates. Genetic studies have demonstrated that both 5' and 3' UTRs are essential for HCV RNA replication. We hypothesize that the conserved 5' and 3' UTRs contain cis-acting RNA elements important for control of HCV RNA replication. The highly conserved 5'UTR harbors two distinct RNA elements, a short 5'-proximal RNA element with a stern-loop structure and a longer element of internal ribosomal entry site (IRES). To determine cis-acting RNA elements in the 5'UTR and to define their roles in HCV RNA replication, we will perform systematic mutagenesis analyses of the conserved sequences/structures by nucleotide deletions, substitutions, and replacement with non-HCV IRES. The 3'UTR consists of three distinct regions, a highly conserved 98 nucleotides that form three stern-loop structures, a poly(U/C) tract of variable length, and a variable region at immediate downstream of the ORF. Cis-acting RNA elements in the 3'UTR for HCV RNA replication will be defined by nucleotide deletions and substitutions. The effects of mutations in the 5' and 3' UTRs on HCV RNA replication will be determined by using reverse genetics systems. We have developed a DNA-based HCV replicon replication system. We have also demonstrated that a DNA-based HCV 'minigenome' RNA was replicated when active replicase complex was provided in trans. These reverse genetics systems for HCV RNA replication will be used to determine cis-acting RNA elements in the 5' and 3' UTRs and their roles in HCV RNA replication. Information gained from these studies will immediately contribute to our understanding of the molecular mechanism of HCV RNA replication and provide meaningful insights to the design of effective strategies for controlling HCV infection.

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- **Project Title: CLINICAL AND LABORATORY STUDIES OF MALIGNANT LYMPHOMAS**

  Principal Investigator & Institution: Levy, Ronald; Professor; Medicine; Stanford University Stanford, Ca 94305

  Timing: Fiscal Year 2002; Project Start 01-APR-1986; Project End 31-MAR-2005

Summary: The goal of this program is to improve the understanding, treatment and survival of patients with malignant lymphoma. We plan to extend our preliminary findings and take advantage of our extensive patient population and tissue bank use and data base. A highly interactive group of investigators will share resources and apply exciting new developments in technology in three general areas. I. Clinical Trials Two clinical trials will be conducted, one for patients with post transplant lymphoproliferative disease and one for patients with mycosis fungoides. These trials will test novel therapeutic approaches developed at Stanford, monoclonal anti CD20 antibody and vaccination with the antigen receptor, respectively. II. Lymphomagenesis The role of **hepatitis C virus** in B cell activation will be investigated. This is based on the discovery that CD81, a molecule important in B cell signaling and in B cell-T interaction, is a receptor for the hepatitis C CD81, a molecule important in B cell signaling and in B cell-T cell interaction, is a receptor for the **hepatitis C virus** coat protein. The immunoglobulins from B cell lymphomas which occur in patients infected with HCV will be tested for binding activity against HCV. The role of the Notch signaling pathway is lymphomagenesis will be studied. The Notch1 gene was found to collaborate with the E2A-PBX1 translocation in T cell lymphoma development in mice. An exciting hypothesis is that a ligand for the Notch1 gene plays an important role in suppressing oncogenesis. III. Gene Expression Patterns in Lymphoma DNA microarrays of genes expressed in lymphocytes (Lymphochips) will be used together with powerful informatics tools to develop new approaches to diagnose, predict outcome, understand tumor progression and analyze signaling pathways in lymphoma.

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- **Project Title: DENDRITIC CELL TARGETED HEPATITIS C VIRUS IMMUNOTHERAPY**

  Principal Investigator & Institution: Mohamadzadeh, Mansour; Medicine; Tulane University of Louisiana New Orleans, La New Orleans, La 70112

  Timing: Fiscal Year 2002; Project Start 27-SEP-2002; Project End 31-AUG-2004

  Summary: (provided by applicant): Hepatitis C is one of the worlds most pandemic and insidious diseases. Less than 41% of patients respond to the current treatment, and a large fraction is ineligible for therapy. Thus, there is an urgent need for new therapeutic strategies. Clearance of **hepatitis C virus** (HCV) is correlated with the level of HCV-specific CD4+ T cells, and viral escape mutations have been identified in immunodominant CD4+ T-cell epitopes. These results suggest that an immunotherapy designed to increase and broaden HCV-specific CD4+ T cells could provide a new therapeutic approach. Dendritic cells (DCs), the most important class of professional antigen presenting cells, possess the ability to elicit both humoral and cellular immune responses. These cells are poised to capture pathogens, migrate to draining lymph nodes, and select antigen-specific CD4+ T cells to regulate T, B, and NK cells, all of which may contribute to protective immunity. The objective of this proposal is to develop a novel vaccine strategy targeting the HCV nonstructural protein 3 (NS3) directly to DC subsets, e.g., Langerhans Cells (LCs). Recently we showed that LCs can be generated by culturing monocytes with GM-CSF+IL15. Such LCs induce significant T-cell activation in vivo. Furthermore, we have generated peptides that bind specifically to LCs or interstitial DCs from a phage display peptide library. We hypothesize that targeting NS3 directly to DCs will increase the level and duration of specific immune responses. Thus, we will target NS3 to DCs by coupling or fusing it to DC-specific peptides. We further hypothesize that NS3 can be structurally modified in order to eliminate the immunodominant epitopes and therefore recruit new T cells against HCV.

Specific aims are: 1) To determine whether targeting NS3 specifically to DC subsets enhances specific immune responses against HCV by analyzing T-cell proliferation/activation in humanized SCID mice; and 2) To augment the development of IFN3 gamma-producing NS3-specific CD4+ T cells by engineering the three-dimensional structure of HCV NS3. Alternative modes of loading DC subsets will be explored, including via recombinant Lactobacillus sp. that express and secrete DC-targeted NS3. A needle-less and non-toxic immunotherapy would provide a treatment for hepatitis C patients who currently have none.

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- **Project Title: DETERMINANTS OF HEPATITIS C & E MORBIDITY IN EGYPT**

  Principal Investigator & Institution: Strickland, George Thomas.; Professor & Director of International He; Epidemiology and Prev Medicine; University of Maryland Balt Prof School Baltimore, Md 21201

  Timing: Fiscal Year 2003; Project Start 15-SEP-2000; Project End 31-AUG-2005

  Summary: By using new molecular virological techniques, Non-A Non-B hepatitis patients have now been categorized into those infected with **hepatitis C virus** (HCV), a parenterally transmitted flavivirus, and hepatitis E virus (HEV), a fecal-oral transmitted "hepatitis E-like virus." WHO estimates that 170 million are infected with HCV, the most common cause of chronic viral hepatitis (CVH), post-necrotic cirrhosis of the liver and hepatocellular carcinoma (HCC). HEV is primarily transmitted in developing countries where it is the most common cause of acute viral hepatitis (AVH) and fulminating hepatitis, particularly in pregnant women. We and others have documented that the highest prevalence of HCV, and also possibly HEV, in the world occurs in Egypt. We have established a Network of Egyptians and Americans who are studying viral hepatitis and its cost to the country. In this ICIDR proposal, we will extend the work of this Network to include investigations of: (1) the effect that the host genome has on chronicity and cirrhosis following HCV infection (Project 1); (2) the host, viral, and environmental determinants of HCC and (because HCV is lymphotrophic as well as hepatotrophic) non-Hodgkins lymphoma (NHL, Project 2); and the epidemiology and complications of HEV (Project 3). Projects 1 & 2 will have case-control studies. The former will compare: (a) chronic carriers of HCV RNA vs. subjects who clear infection and (b) those with HCV who develop cirrhosis vs. those that show no signs of disease; while the latter compares HCC or NHL cases vs. age- and gender-matched controls. Projects 1-3 will have prospective cohort studies of 10,000 inhabitants of two villages with prevalence of anti-HCV of 9% and 24% and anti-HCV of 51 and 70%, respectively. Their goals will be to determine incidence of, and risk determinants for cirrhosis (Project 1), HCC and NHL (Project 2), and HEV infection and disease (Project 3). A cohort of pregnant women and children will be studied to assess HEV morbidity in pregnancy and exposures and disease in infancy. Domestic animals and peri-domestic rodents will be studied to determine whether HEV has a zoonotic component in Egypt. Viral genotypes, host class I and II alleles and candidate genes, e.g., chemokine receptors and HDL, a possible HCV receptor, and environmental exposures and their impact on host genes (p53 genetic fingerprinting) will be assayed. Because the scientific, administrative, logistic and laboratory network is in place and both HCV and HEV have such a high prevalence in Egypt, these investigations have a high probability of early success. Explanations for these very important questions can be obtained at a fraction of the cost and time as they could be found elsewhere, and the results should lead to the development of better interventions to prevent the two most important causes of liver disease in the world.

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- **Project Title: DEVELOPING MURINE MODELS OF HCV REPLICATION**

  Principal Investigator & Institution: Uprichard, Susan L.; Scripps Research Institute Tpc7 La Jolla, Ca 92037

  Timing: Fiscal Year 2003; Project Start 30-SEP-2003; Project End 31-AUG-2005

  Summary: (provided by applicant): With approximately 2% of the world population infected, **Hepatitis C Virus** (HCV) has emerged as a significant public health problem creating a significant medical, social, and economic burden. Between 70- 90% of those infected fail to clear the virus and remain chronically infected with the likelihood of progression to persistent hepatitis, liver cirrhosis, and hepatocellular carcinoma (HCC). As a result, HCV-associated liver disease is the leading cause of liver transplantation in the United States. At this time, no preventative vaccine is available, and only 20-30% of chronically infected patients respond to the currently available therapy. Hence, there is a pressing need for a preventative vaccine and alternative treatment options. Unfortunately, research efforts to understand, and thus combat, this infection have been hindered by the lack of robust tissue culture replication systems and small animal models. While the recent development of the in vitro HCV replicon system has overcome some of these limitations, small animal models are still needed for the study of viral-host interactions to assess the pathological effects of the virus and to better understand HCV immunology (e.g. the immunological and virological basis of recovery versus persistence), as well as for testing the in vivo potential of physiological and pharmacological agents for controlling HCV infection. Therefore, the objective of this exploratory proposal is to create mouse models capable of expressing, and potentially replicating, HCV. Initial efforts will focus on the use of selectable HCV replicons, which have proven to be an efficient HCV replication system. However, the mouse-adaptation information gained in these studies may subsequently allow for the development of analogous models that replicate native HCV genomes. The Specific Aims to be addressed are: 1) determine if HCV species tropism can be altered by adapting currently available HCV replicons to replicate in mouse hepatocytes; 2) determine if a murine model of acute HCV can be established by transient T7-driven expression of HCV construct(s) in vivo; and 3) determine if stable RNA Polymerase I-driven expression of HCV construct(s) can serve as a chronic murine model of HCV in vivo.

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- **Project Title: DEVELOPMENT OF HEPATITIS C VIRUS ENTRY INHIBITORS**

  Principal Investigator & Institution: Gardner, Jason P.; Progenics Pharmaceuticals, Inc. 777 Old Saw Mill River Rd Tarrytown, Ny 10591

  Timing: Fiscal Year 2002; Project Start 15-SEP-2002; Project End 31-AUG-2004

  Summary: (provided by applicant): The development of new therapeutic agents for **hepatitis C virus** (HCV) infection is a major public health priority. We have selected HCV entry as a target for the discovery and development of novel antiviral agents. The overall goal of this Phase I project is to develop a novel cell-based membrane fusion assay that accurately recapitulates HCV entry, using well characterized, biologically relevant cellular reagents.During the Phase I project, we will develop stable cell lines that express fusogenic forms of native HCV envelope glycoproteins, and use these cells to adapt a cell-based membrane fusion assay for HCV entry. We will generate stable human hepatocyte cell lines as appropriate targets for fusion, and optimize the assay for reproducibility, sensitivity and suitability for high-throughput screening (HTS). We will

also probe the mechanism of HCV entry using monoclonal antibodies and cell lines expressing putative attachment receptors.Success in the Phase I project will enable the HCV membrane fusion assay to be utilized in Phase II for HTS of libraries of structurally diverse small molecules, in order to identify potent inhibitors of HCV entry. Lead compounds will be screened for in vivo inhibition of HCV infection in a novel transgenic mouse model and mechanisms of action will be probed. Promising compunds will be developed for clinical application for HCV infection.

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- **Project Title: DEVELOPMENT OF PREVENTATIVE AND THERAPEUTIC HCV VACCINES**

  Principal Investigator & Institution: Milich, David R.; President; Vaccine Research Institute of San Diego San Diego, Ca 92109

  Timing: Fiscal Year 2003; Project Start 30-SEP-2003; Project End 31-MAR-2007

  Summary: (provided by applicant): The overall objective of this proposal is to develop **hepatitis C virus** (HCV)-specific immunogens that may be useful as prophylactic and/or therapeutic vaccines for the prevention or treatment of chronic HCV infection. Two general nonexclusive approaches are proposed. In the first approach (Specific Aim 1) we propose to develop a prophylactic HCV vaccine designed to elicit neutralizing antibodies to the HCV E2 protein. For this purpose we have developed the woodchuck hepatitis core protein (WHcAg) as a particulate vaccine carrier platform. The WHcAg platform is capable of accommodating a variety of inserted B cell and CD4 + T cell epitopes and elicits extremely high levels of antibodies to the inserted B cell epitopes and primes insert-specific CD4 v T cells. Three categories of E2-specific neutralizing B cell epitopes will be inserted into the WHcAg vaccine platform: (a) highly conserved, non-HVR1 E2 epitopes that we have identified; (b) consensus sequences derived from the highly variable HVR1 region of E2, which will address the problem of genetic variability of HCV; and (c) conserved "framework motifs" present within the HVR1 region. The E2- WHcAg hybrid particles will be optimized for protein expression, assembly competence, yield in the E. coil expression system, antigenicity and immunogenicity. Because strong T cell responses (both CD4 vand CD8 v) against HCV antigens and especially the nonstructural 3 (NS3) protein have been linked to viral clearance in acute and chronic HCV infection, our second approach will be aimed at developing a NS3/4A-specific DNA vaccine candidate (Specific Aim 2). The NS3 protein is highly conserved and an advantage of a DNA vaccine is the ability to elicit CD4 v Th cells and CD8 v CTL as well as antibody. We have found that a NS3/4A gene elicits significantly more efficient immune responses than the widely used NS3 gene. It is anticipated that a NS3/4A DNA vaccine may be used for prophylactic or therapeutic applications either alone or in combination with E2-WHcAg hybrid particles.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: DIAGNOSTIC FLOW CYTOMETRY**

  Principal Investigator & Institution: Kaplan, David R.; Associate Professor; Flow-Amp Systems, Ltd 11000 Cedar Ave Cleveland, Oh 44106

  Timing: Fiscal Year 2002; Project Start 30-SEP-2002; Project End 31-MAR-2004

  Summary: (provided by applicant)Hepatitis C virus infection is a chronic disease that inflicts 170 million people worldwide. Infection usually results in a persistent hepatitis that can lead to cirrhosis and/or hepatocellular carcinoma. Moreover, chronic infection is associated with a number of adverse complications including lymphoma and

autoimmune phenomena.Besides hepatocytes, the virus has been shown to infect peripheral blood cells. Investigators have suggested that infection of lymphocytes may be related to the development of lymphoma and autoimmune phenomena, to the progression of the chronic infection, and to maternal-fetal transmission of the virus. Although there are excellent diagnostic tests for **hepatitis C virus,** the currently available tests do not predict progression, maternal-fetal transmission, or immunologically related complications.We have developed an ultra-sensitive technology for the detection of molecules expressed in single cells and analyzed by flow cytometry. This technology, enzymatic amplification staining, has achieved 10-100 fold enhancements in fluorescence intensity which has been used to detect the presence of molecules that could not be detected by standard immunofluorescent methods.We propose in this grant application to assess the presence of HCV proteins and/or nucleic acids in cells infected in vitro with enzymatic amplification staining. The successful development of this capability will prompt an analysis of its utility in assessing patient samples.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: EARLY DETECTION OF LIVER CANCER AND HEPATITIS**

  Principal Investigator & Institution: Block, Timothy M.; Professor and Director; Biochem & Molecular Pharmacol; Thomas Jefferson University Office of Research Administration Philadelphia, Pa 191075587

  Timing: Fiscal Year 2002; Project Start 30-SEP-1999; Project End 31-AUG-2004

  Summary: The goal of this proposal is to develop methods for the early detection of hepatocellular carcinoma (HCC) and hepatitis. The hypothesis that changes in the amount or modification of serum polypeptides correlate with the onset of HCC or hepatitis will be determined. Individuals chronically infected with hepatitis B or C virus (HBV, HCV) are at high risk for the development of HCC and hepatitis, with disease progression occurring after many years. Serum polypeptides from individuals at different stages in the disease continuum will be resolved by "Proteomic" 2-dimensional gel analysis. Our preliminary evidence and the work of others demonstrate that 2D gel technology has advanced to the point where expressed protein profiles of biological samples can be reproducibly resolved. Polypeptides that correlate (by their appearance, disappearance or post translational modification) with disease status will be identified. Correlating polypeptides will be characterized by a variety of methods available to us: data base reference, immunological methods or micro sequencing. Identification of biomarkers that help in the diagnosis and prediction of liver disease in this high-risk population will have enormous public health benefit, given the limitations on current methods. It will also provide insights about the mechanisms of progression of this disease family and offer a platform technology for the use of proteome diagnostics in other areas of cancer detection and liver decompensation.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: ENZYMATIC DIFFERENCES AMONG HEPATITIS C VIRUS GENOTYPES**

  Principal Investigator & Institution: Frick, David N.; Biochem and Molecular Biology; New York Medical College Valhalla, Ny 10595

  Timing: Fiscal Year 2003; Project Start 15-FEB-2003; Project End 31-JAN-2008

  Summary: (provided by applicant): Almost one in every fifty-five Americans have been exposed to the **Hepatitis C Virus** (HCV), but most are unaware of their infection

because the virus causes few acute symptoms. If left untreated, the majority of HCV infections lead to chronic active hepatitis that eventually progresses to cirrhosis, cancer, or liver failure. Current therapies involving the drugs interferon and ribavirin are costly and produce debilitating side effects, frequently worse than the symptoms produced by HCV itself. Newer treatments are, however, quite effective against certain viral genotypes. This proposal will examine the HCV proteins most directly involved in viral replication, the NS3 Helicase and NS5B polymerase, as putative targets for the drug ribavirin and as targets for new antiviral agents. In addition to its established role as a modulator of the immune system, ribavirin has been proposed to eliminate viruses as a mutagen or through direct effects on viral replicative proteins. One popular hypothesis states that ribavirin's enhancement of the already high HCV mutation rate leads to a catastrophe of errors and subsequent virus elimination. Here, ribavirin effects will be examined in vitro, in enzyme assays, and in vivo, using a novel HCV replicon that should allow the assessment of replication fidelity. To attempt to relate ribavirin effects to genotype-specific drug response, all experiments will be repeated with the three most common American HCV genotypes, two that normally do not respond to therapy (la and lb) and one that frequently responds to therapy (2a). The polymerase and helicase proteins from each genotype will also be characterized to define conserved and divergent properties. A rigorous biochemical approach will be used to define enzyme differences because sequence data alone does not accurately predict protein structure or function. Preliminary data show that different genotypes encode enzymes with markedly different properties, hampering current rational drug design efforts. Structure-based site-directed mutagenesis will be used to determine the genetic basis for HCV enzyme variability. The biological consequences (i.e. replication rate, fidelity, protein expression) of HCV genetic variation will then be analyzed in a replicon system. The delineation of genetic variations responsible for certain phenotypes might allow the prediction of patient response to current or future HCV therapies, and the clear identification of conserved HCV enzyme properties will aid future HCV drug development.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: EPIDEMIOLOGY AND IMPACT OF HEPATITIS C IN THE COMMUNITY**

  Principal Investigator & Institution: Kim, W. R.; Assistant Professor; Mayo Clinic Coll of Medicine, Rochester 200 1St St Sw Rochester, Mn 55905

  Timing: Fiscal Year 2003; Project Start 15-MAR-2003; Project End 31-DEC-2007

  Summary: (provided by applicant): **Hepatitis C virus** (HCV) is the most common chronic blood-borne infection in the US: an estimated 2.7 million Americans have been infected with the virus. Although the prevalence of HCV infection in the population is well established, the public health impact of liver disease caused by HCV remains uncertain. Based on established resources for population-based research in Olmsted County (the Rochester Epidemiology Project), we have already established a registry of all community residents presently diagnosed with HCV. In this study, we propose to screen community residents for HCV and then determine the impact of HCV infection in the community. In Aim 1, we will measure the prevalence of HCV which has not previously been diagnosed by screening the serum of Olmsted County residents of ages 30 to 49 years for HCV. For screening, we will utilize an established method to obtain serum samples from the majority of the target population in the community. In Aim 2, we will compare the prevalence and severity of liver disease, health status, quality of life and comorbidity profile among three groups of community residents, namely those

with established HCV diagnosis, those with HCV infection discovered only by screening, and those without HCV infection. In Aim 3, based on these three groups, we will measure community-wide healthcare resource utilization related to HCV, independent of effects of comorbid conditions, particularly substance abuse and mental health problems. The results of this work will address the substantial gap between patient outcome data derived from referral patient samples and prevalence data based on population surveys, by providing key information about the impact of HCV on morbidity and health of the majority of Americans whose HCV infection remains undetected. My long-term goal is to establish a comprehensive patient-oriented research program in viral hepatitis and liver disease, encompassing epidemiology, survival statistics, quality of life, and health services research. Resources created by the current project, namely detailed clinical information and biologic specimens from a large cohort of community residents with HCV, will provide future opportunities to study natural history, virologic and host prognostic determinants of progression, and effectiveness of community-based interventions on HCV outcomes.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: ETIOLOGY AND PREVENTION OF BLOOD BORNE VIRUSES IN IDUS**

  Principal Investigator & Institution: Hagan, Holly C.; Deputy Director; National Development & Res Institutes Research Institutes, Inc. New York, Ny 100103509

  Timing: Fiscal Year 2002; Project Start 30-SEP-2001; Project End 31-MAR-2007

  Summary: (provided by applicant): The etiology and prevention of blood-borne viral infections in injection drug users (IDUs) have not been fully characterized, and many questions remain regarding which injection practices may result in I infection. Viral hepatitis infections in IDUs are among the most frequently occurring 81ood-bornel l infections in humans; in low HIV-prevalence settings, morbidity and mortality in IDUs attributable to l hepatitis virus infections may exceed that for HIV. **Hepatitis C virus** (HCV) is highly prevalent in IDU- populations, and is more efficiently transmitted l abouty injection than HIV. Because sexual HCV transmission is relatively rare, it may serve as a highly sensitive biologic marker of direct percutaneous exposure to these infections in drug injectors, and may contribute to understanding the mechanism of transmission of other infections via injection practices. The long-term goal of our research is to advance knowledge of the epidemiology, etiology and-prevention of HIV and hepatitis infections in IDUs. We propose studies that will make new contributions toward our long-term goal: Aim 1. Examine the extent to which HCV prevention education at the Seattle needle exchange program has reduced the risk of HCV infection. Aim 2. Measure the risk of HCV seroconversion associated with specific injection risk behaviors, and calculate the risk of HCV attributable to these practices in the IDU-population. Aim 3. Compare reporting of socially-undesirable or stigmatized injection and sexual risk behavior collected by A-CASI to interviewer-administered data collection methods. Aim 4. Assess the feasibility and disease control benefits of HBV and HCV partner notification for IDUs. Aim 5. Study whether changes in hepatitis C reporting laws are associated with increased reporting in IDUs. The significance of this research is its potential contribution to our understanding of the etiology of these l infections, and examines many practical questions related to the effectiveness of public health surveillance and prevention programs.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: FUNCTIONAL ANALYSIS OF HEPATITIS C VIRUS GLYCOPROTEINS**

  Principal Investigator & Institution: Mckeating, Jane A.; Associate Professor; Lab/Virology & Infect Diseases; Rockefeller University New York, Ny 100216399

  Timing: Fiscal Year 2004; Project Start 01-APR-2004; Project End 31-MAR-2009

  Summary: (provided by applicant): **Hepatitis C virus** (HCV) infection is often associated with chronic liver disease, sometimes resulting in cirrhosis and hepatocellular carcinoma. The lack of in vitro systems for HCV propagation has hampered biological studies on the virion and its mechanism(s) of cell entry, and the cellular receptors remain unknown. The selective association of a virus with a target cell is usually determined by an interaction between the viral glycoproteins (gps) and specific cell-surface receptor(s) and is an essential step in the initiation of infection. Such interaction(s) often define the host range and cellular or tissue tropism of a virus and have a role in determining virus pathogenicity. HCV encodes two envelope gps E1 and E2, which accumulate in the endoplasmic reticulum, the proposed site for HCV assembly and budding. In the absence of native HCV particles, truncated version(s) of E2 and virus-like particles expressed in insect cell systems have been used as mimics to study virus-cell interactions. Soluble versions of E2 have identified interactions with CD81, scavenger receptor class B type 1 and DC-SIGN. However, these studies only measure HCV gp-cell attachment and not virus mediated cell fusion. To overcome the lack of a conventional cell culture system for the propagation of infectious HCV particles, we have developed retroviral pseudotypes which incorporate native HCV gps. These pseudotypes are infectious for human liver-derived cell lines and their infectivity is pH-dependent and neutralized by monoclonal antibodies specific for E2 and CD81. HepG2 cells can be rendered permissive for HCV pseudotype infection when engineered to express CD81, demonstrating that CD81 is a component of the receptor complex. This system will allow us to study HCV gp interaction(s) with target cells and to identify the cellular molecules involved. In addition, we will address whether neutralizing antibodies are elicited during HCV infection and whether they correlate with resolution or control of disease.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: FUNCTIONAL GENOMICS AND HCV-ASSOCIATED LIVER DISEASE**

  Principal Investigator & Institution: Katze, Michael G.; Professor; Microbiology; University of Washington Grant & Contract Services Seattle, Wa 98105

  Timing: Fiscal Year 2002; Project Start 30-SEP-2002; Project End 31-MAY-2007

  Summary: (provided by applicant): In this application for a Core Support Center, we propose to apply the technologies of functional genomics to the study of **hepatitis C virus** (HCV)-associated liver disease, a public health problem that is a direct consequence of drug abuse and addiction. This center will be composed of a diverse group of NIH-funded investigators, including experts in viral hepatitis, liver disease and transplantation, global gene expression analysis, proteomics, and advanced information technologies. The unifying theme is the desire to gain a detailed understanding of the molecular mechanisms underlying the progression from chronic HCV infection to end-stage liver disease, including cirrhosis and hepatocellular carcinoma. The University of Washington provides an exceptional environment that has fostered a high level of expertise in all these venues, and it is only through a Core Support Center that such a multidisciplinary group of researchers can be brought

together to focus their expertise on a single problem. The proposed center will consist of four cores: Microarray & Virology, Proteomics & Modeling, Bioinformatics & Biostatistics, and Administration. Investigators from basic and clinical science will participate in the Microarray & Virology Core, providing a primary human hepatocyte cell culture system and access to unique patient populations, including biopsy material from patients with recurrent HCV after liver transplantation, and from patients co-infected with HCV and human immunodeficiency virus. An established infrastructure is in place for microarray analysis, including extensive experience in gene expression analysis during virus infection. The Proteomics & Modeling core will be located at the Institute for Systems Biology, one of the world's leading proteomics centers. Specialists in computational biology, bioinformatics, and statistics will provide the essential functions of data management, analysis, and statistical evaluation. This group will also develop a national database resource of gene expression and proteomics data that can be accessed via the World Wide Web. This multidisciplinary approach provides a unique opportunity to advance our understanding of viral hepatitis and liver disease to a level far in excess of that which could be obtained by any of these investigators working individually. The Core Support Center provides the mechanism to bring this outstanding group of scientists together and to attract additional scientists of the highest quality.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: HCV GENOMIC VARIABILITY IN HIV INFECTED HEMOPHILIACS**

  Principal Investigator & Institution: Sherman, Kenneth E.; Professor of Medicine; Internal Medicine; University of Cincinnati 2624 Clifton Ave Cincinnati, Oh 45221

  Timing: Fiscal Year 2002; Project Start 01-JUN-2001; Project End 31-MAY-2005

  Summary: Hemophiliacs with symptomatic disease are multiply exposed to blood products including factor concentrates to correct the Internet clotting factor deficiencies. Prior to routine use of heat inactivation and screening of donor blood for specific viral pathogens, hemophilia patients were routinely exposed to, and infected with, viruses such as hepatitis B (HBV), hepatitis C (HCV) and human immunodeficiency virus (HIV). Cohort studies in hemophiliacs suggest several clinically and scientifically important findings that warrant further detailed investigation including; a) Liver disease progression may be altered in hemophiliacs infected with HCV with more rapid progression to liver failure and death; b) The source of infection from large pools of concentrate that were potentially infected by multiple discreet donors leads to a high risks of mixed infection represented by both genotype and quasi species heterogeneity; c) The HIV coinfected hemophiliacs may have different clinical outcomes and an altered immune response may facilitate our understanding of the underlying process of mutant virus selection, and the associated clinical outcomes. The overall goals of this proposal include the study and characterization of the genomic RNA of HCV in infected hemophilic patients with and without confection with HIV. In the retrospective Phase 1, we utilize the NCI Multi center Hemophiliac Cohort Study serum bank database to study the relationship between progression to decompensated liver disease and quasi species variability in the viral envelope hyper variable and core domain. Heteroduplex analysis will be used to rapidly screen samples from index patients and matched controls using samples longitudinally collected over a 10 year or longer period of time. Peptides will be produced from unique quasi species and these peptides will be evaluated for their function as CTL epitomes. Phase 2 involves the initiation and performance of a clinical intervention trial designed to determine variable kinetic response rates to PEG-interferon+ribavirin between hemophiliacs with HCV alone vs

HCV/HIV coinfected subjects. Quasi species populations will be modified/cloned, sequencing will be performed to generate families of closely related core peptides that will be studied for their ability to bind and stimulate an immune response. Treatment nonresponders will be followed in a prospective cohort study for up to 3 additional years so that the evolution of the virus, and its associated immune response in this group can be evaluated.

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- **Project Title: HCV INFECTION--RISK FACTORS FOR PROGRESSION**

  Principal Investigator & Institution: Stuver, Sherri O.; Assistant Professor; Epidemiology; Harvard University (Sch of Public Hlth) Public Health Campus Boston, Ma 02115

  Timing: Fiscal Year 2002; Project Start 01-AUG-2001; Project End 31-JUL-2006

  Summary: (provided by applicant): For individuals who are infected with **hepatitis C virus** (HCV), knowledge of co-factors affecting the occurrence of liver disease is crucial. However, the mechanisms of HCV-associated pathogenesis, particularly with regard to the role of the virus and the host immune response, remain unclear. The primary goal of the proposal is to elucidate the natural history of HCV infection with respect to progression to hepatocellular carcinoma (HCC) and other health outcomes in a Japanese community-based population in which infection with HCV is highly endemic. As part of an annual ultrasonographic tomography screening program in this population, nearly 1,000 adult residents with HCV have been under surveillance for liver cancer since 1994. The proposed study will extend the observation of this cohort, with the additional collection and analysis of virologic, epidemiologic, and clinical data. The specific aims of the research are: to determine the predictive value of markers of HCV infection in the development of liver damage and HCC; to estimate the effect of host-related factors, including heavy alcohol consumption, cigarette smoking, and diet, on HCV-induced liver disease progression and hepatocarcinogenesis; to examine the role of co-infection with hepatitis B virus and human T-lymphotropic virus type I in the natural history of HCV; to characterize the function of host immune status and response in the persistence of HCV infection as well as in the progression of liver disease and HCC among HCV carriers; to evaluate the utility of serologic markers of liver damage in predicting the development of HCC in individuals infected with HCV; to identify predictors of extrahepatic morbidity and mortality among HCV carriers. The uniqueness of the study population and the richness of the data parameters combined with the extensive experience of the assembled multi-disciplinary team provide an important opportunity to increase our understanding of the natural history of HCV and to contribute to our ability to identify and potentially treat those carriers who are at increased risk of an adverse outcome related to their HCV infection.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: HCV NS5A: MOLECULAR VIROLOGY AND ANTIVIRAL TARGET**

  Principal Investigator & Institution: Glenn, Jeffrey S.; Medicine; Stanford University Stanford, Ca 94305

  Timing: Fiscal Year 2004; Project Start 01-JAN-2004; Project End 31-DEC-2008

  Summary: (provided by applicant): **Hepatitis C virus** (HCV) is a major cause of viral hepatitis. There is no effective therapy for most patients. Our long-term objectives are to understand the molecular virology of HCV and translate this knowledge into new antiviral strategies. Like other positive-strand RNA viruses, HCV is believed to replicate

in association with cytoplasmic membranes, although the mechanistic details remain unknown. NS5A, one of the virus' non-structural proteins appears to play a key role in this process. How NS5A is localized to its restricted subset of host cell cytoplasmic membranes has been provocative considering it lacks features commonly responsible for the membrane association of proteins. An amphipathic helix (AH) has recently been identified in the N-terminal domain of NS5A. This structural motif is necessary and sufficient for membrane localization. An amphipathic helix is conserved across HCV isolates. Genetically disrupting the amphipathic helix-mediated localization of NS5A impairs replication of HCV RNA. These results have exciting implications with respect to the role of NS5A in the HCV life cycle, HCV's interaction with its host cell, and the design of novel anti-HCV therapies. We hypothesize: 1) the minimal elements required for membrane association or RNA replication can be further narrowed to a subset of amino acids within the AH; 2) the association is mediated in part by a protein partner in the targeted membranes; 3) mislocalization of NS5A affects the assembly of other components of the RNA replication complex; 4) an HCV genome encoding a mutated NS5A AH can be complemented in trans; 5) the membrane association of NS5A can be pharmacologically disrupted. We will test these hypotheses by using mutagenesis, immunomicroscopy, and in vitro membrane association assays to identify the critical viral and host features required for NS5A membrane association. These methods will also be used to determine how other components of the replicase complex are linked to NS5A's membrane association. Molecular genetics with HCV replicons will be used to define NS5A's cis and trans functions in RNA replication. We will use phage display to identify high affinity random peptide ligands of the AH. Finally, we will explore how our results can be translated into novel anti-HCV strategies.

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- **Project Title: HCV, HIV AND OPIOIDS: CELLULAR INTERACTIONS**

  Principal Investigator & Institution: Ho, Wenzhe; Professor; Children's Hospital of Philadelphia 34Th St and Civic Ctr Blvd Philadelphia, Pa 191044399

  Timing: Fiscal Year 2002; Project Start 27-SEP-2002; Project End 31-JUL-2005

  Summary: (provided by applicant): This is a R21 application in response to RFA-DA-02-008. Injection drug users (IDUs) are the single largest risk group for **hepatitis C virus** (HCV) infection and the co-infections with human immunodeficiency virus (HIV) and HCV are frequently found in IDUs. These two pathogens are also likely to be responsible for the highest infectious disease morbidity and mortality rates among IDUs. The general aim of this study is to determine the role of opioids (e.g., morphine) in the immunopathogenesis of HCV disease in the presence or absence of HIV infection. We hypothesize that opioids, through their receptors on human hepatocytes and immune cells, modulates HCV infection and replication. We will use both in vitro and in vivo models to directly address the question whether opioids have the ability to enhance HCV infection and replication. We seek to understand how HCV and HIV modify each other's replication in both in vitro and in vivo systems. We propose four specific aims: 1) We will determine whether opioids such as morphine enhances HCV infection of and replication in primary human hepatocytes, hepatoma cell lines (HepG2, Huh-7) and T cell lines (MT-2 and MT-2C); 2) We will determine whether opioids have the ability to induce HCV RNA expression in HCV replicon containing human hepatoma cell lines (Huh.5 and Huh.8). We will also examine whether HCV has ability to infect chronically HIV infected human T and monocytic cell lines (ACH-2, J 1.1 and U 1); 3) We will determine whether the removal of CD8+ T cells from PBMCs, and opioids, when added to CD8+ T cell-depleted PBMC isolated from HCV and/or HIV-infected subjects, induce

HCV replication. In addition, we will examine whether HIV induces HCV replication in PBMCs isolated from HCV/HIV coinfected subjects; 4) We will determine plasma and PBMC HCV RNA levels in HCV and/or HIV-infected subjects attending methadone program. We will directly measure the levels of HCV RNA in plasma and PBMC using our newly developed real time RT-PCR assay. The investigation of the impact of opioids on HCV infection and its interaction with HIV will contribute to our basic understanding of host defense processes and the role of drug abuse in HCV and/or HIV infection of human liver and immune cells, ultimately further the design and development of improved treatment for drug-abusing patients infected with HCV and/or HIV.

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- **Project Title: HEPATIC STELLATE CELL ACTIVATION INDUCED BY HCV**

  Principal Investigator & Institution: Brenner, David A.; Professor; Medicine; Columbia University Health Sciences Po Box 49 New York, Ny 10032

  Timing: Fiscal Year 2003; Project Start 30-SEP-2003; Project End 31-AUG-2008

  Summary: (provided by applicant): **Hepatitis C virus** (HCV) infection is the main cause of chronic liver diseases in the US. Current antiviral treatments only cure the infection in half of the patients. The remaining patients often develop progressive hepatic fibrosis, leading to cirrhosis and hepatocellular carcinoma. These patients are sensitive to the hepatotoxic effects of alcohol, since moderate alcohol consumption accelerates fibrosis progression. Unfortunately, there are no effective antifibrotic treatments for patients with chronic liver diseases. The overall goal of this project is to define the mechanisms by which HCV leads to liver fibrosis and to identify potential targets of therapy. We will also investigate the mechanisms by which alcohol consumption aggravates the effects of HCV. We will use recently developed tools to express the HCV in the mouse liver and in liver cells and a well-characterized model of alcohol-induced liver injury. This proposal is based on several underlying hypotheses: 1) HCV directly interacts with hepatic stellate cells (HSCs), the main fibrogenic cell type, to induce liver fibrosis; 2) Fibrogenic products from hepatocytes expressing the HCV replicon induce fibrogenic actions in HSCs; 3) Alcohol administration induces the development of liver fibrosis in transgenic mice expressing the whole HCV genome; and 4) HSCs isolated from patients with HCV induced liver cirrhosis show phenotypical and functional features of activated HSCs and non-parenchymal liver cells are infected by HCV in patients. The specific aims to be addressed in this project are: 1) To determine whether HCV proteins induce fibrogenic actions in primary cultured HSCs; 2) To determine whether hepatocytes and lymphocytes expressing the HCV induce fibrogenic actions in HSCs; 3) To investigate the mechanisms by which alcohol consumption aggravates HCV-induced liver fibrosis; and 4) To investigate the phenotypical and functional features of HSCs isolated from patients with HCV-induced liver cirrhosis and whether non-parenchymal liver cells are infected by HCV in patients. The experimental design will use primary cultures of HSCs, cultured cells expressing the HCV genomic replicon, and transgenic mice expressing the whole HCV genome in the liver. By combining in vivo and in vitro studies, our goal is to discover new insights into the molecular pathogenesis of HCV-induced liver fibrosis.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: HEPATITIS B AND C AMONG HOMELESS ADULTS**

  Principal Investigator & Institution: Gelberg, Lillian; Family Medicine; University of California Los Angeles 10920 Wilshire Blvd., Suite 1200 Los Angeles, Ca 90024

Timing: Fiscal Year 2002; Project Start 01-JUL-2001; Project End 31-MAY-2004

Summary: Applicant's Abstract Persons infected with the hepatitis B virus (HBV) or **hepatitis C virus** (HCV) are at high risk for serious long-term health problems, and they are potentially infectious to others. Because of the seriousness of these infections, the NIH has developed a national agenda for preventing the spread and consequences of HBV and HCV. This agenda includes early detection, treatment, and prevention efforts for high-risk and infected persons. Homelessness has reached crisis proportions in the US today. Recent research by our team and others suggests that homeless adults in urban areas are a group at particularly high risk for HBV and HCV infections due to high rates of risky drug use and risky sexual behaviors. Despite the apparent high risk, however, there is only limited research on viral hepatitis in this group. We propose to conduct epidemiologic and health services research regarding HBV and HCV in a population-based sample of 500 homeless adults. We will recruit a probability sample of homeless adults with oversampling of injection drug users from 30 shelters and meal programs in the Skid Row area of Los Angeles. Respondents will undergo a two-hour interview (including the Diagnostic Interview Schedule-DIS-IV) and blood draw for hepatitis serology. We will estimate the prevalence of HBV and HCV and identify risk factors for each. We will evaluate whether homeless adults with histories of injection and non-injection drug use, risky sex, serious alcohol or mental disorders, or chronic homelessness have an elevated risk for these infections. We will also conduct health services research in which we will describe the respondents' past history of HBV/HCV testing, awareness of infection status, medical care for HBV and HCV, and willingness to return for HBV/HCV test results. Further, we will identify utilization of medical and non-medical settings to identify sites for future screening, treatment, and prevention efforts. We will provide hepatitis B immunization to those that test negative for hepatitis B. We will bridge the gap between research and prevention by using the Theory of Planned Behavior to understand protective behaviors used by homeless adults to avoid exposure to infectious diseases.

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- **Project Title: HEPATITIS C CLEARANCE AND HOST GENETIC FACTORS**

  Principal Investigator & Institution: Thio, Chloe L.; Assistant Professor; Medicine; Johns Hopkins University 3400 N Charles St Baltimore, Md 21218

  Timing: Fiscal Year 2002; Project Start 30-SEP-2000; Project End 31-AUG-2005

  Summary: (Applicant's Abstract) The candidate is completing a three year Infectious Diseases fellowship and has devoted the last two years to studying associations of the human leukocyte antigen complex to hepatitis B virus outcomes in a multi-cohort study. Through this grant, the candidate will use molecular genetics tools in an epidemiologic setting and will thus bridge the gap between the epidemiologists and basic scientists in an effort to understand immunopathogenic mechanisms of infectious diseases. Long-term, the candidate would like to establish herself as a faculty member interested in understanding infectious disease outcomes by examining the genetically-determined variability of the host response. In particular, in the short-term, this candidate is interested in studying host genetic factors that affect hepatitis C outcomes to elucidate mechanisms of **hepatitis C virus** pathogenesis, which eventually may have therapeutic and vaccine implications. The work will be performed under the guidance of Dr. David Thomas who has expertise in hepatitis C and epidemiology. In collaboration with Dr. David Vlahov, the epidemiologist who established the ALIVE cohort, and with Dr. Mary Carrington, a leader in the field of genetics, the candidate will have the collaborative resources necessary for the successful completion of this project. The candidate will

complement her research by attending 2 hours per week of infectious diseases and hepatitis related conferences, attending weekly hepatitis C research meetings, and seeing patients in an infectious diseases/hepatitis clinic one half-day per week. She also plans to take courses in epidemiology, genetics, and virology. Over 170 million people worldwide are infected with **hepatitis C virus** (HCV), 85 percent of them have a persistent infection and the remainder clear the virus. This heterogeneous outcome difference is not explained by viral or environmental factors. As has been shown in other chronic viral infections, it is likely that host factors, which may be genetically programmed determine these outcomes. In the past, these host-virus interactions have been difficult to explore because of limited knowledge of HCV biology and lack of molecular tools to explore the human genome. However, HCV biology is unfolding and the recent advances in molecular biology permit detection of human genomic variability on a large scale. Using the ALIVE cohort of injection drug users, the candidate will study 131 individuals who have cleared the virus and 262 matched controls with persistent HCV infection. She will test polymorphisms in the human leukocyte antigen alleles and putative pathogenic genes for distortions in allele frequency between the clearance and persistently infected individuals. Where possible, the allele frequencies will be checked for Hardy-Weinberg equilibrium distortions. Chi-square analysis and univariate and multivariate conditional logistic regression will be performed. The associations will also be assessed with regards to HCV genotype. Success is anticipated since the cohort is well-characterized, the molecular tools exist, and the collaborations have proven to be productive in HBV studies.

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- **Project Title: HEPATITIS C IN CENTRAL EUROPE**

  Principal Investigator & Institution: Krekulova, Laura; Nusle Clinic Taborska 57 Prague,

  Timing: Fiscal Year 2003; Project Start 01-JUL-2003; Project End 31-DEC-2007

  Summary: (provided by applicant) This is a reentry grant proposal being submitted by an investigator who has undergone Fogarty International Center (FIC)-supported training at the University of California, Berkeley in molecular epidemiology of viral hepatitis. The study will focus on hepatitis C in Prague, Czech Republic. Hepatitis C is a major emerging infectious disease problem in Central and Eastern Europe, especially among young adults who engage in injection drug use (IDU) practice. IDU practice itself has become an epidemic in the last 10 years in Prague, Czech Republic. We wish to take advantage of this epidemic to characterize the natural history, clinical response to therapy, and epidemiology of hepatitis C in Prague. One unique feature of the current hepatitis C epidemic in Prague is that the hepatitis C viral (HCV) subtype diversity is limited, compared to those cities in the US or Western Europe, where IDU has been in practice for a much longer time. Hence, we wish to determine if any sets of viral strain types can be shown to be associated with adverse clinical outcome and response to antiviral therapy. To do so, we plan to 1) compare prospectively HCV genotype and subtype distribution, and evolution of the viral subtypes among cohorts of IDU and non-IDU subjects undergoing treatment for HCV infection in Prague, and determine if such characteristics are associated with certain treatment outcomes; 2) study the natural history of the HCV epidemic among untreated IDU populations for viral subtype distribution, evolution, and clinical outcomes among newly infected subjects in Czech Republic; and 3) create a registry of a database related to viral strain type, patient clinical characteristics, and therapeutic response rates that may be used to evaluate the long-term consequences of HCV infection (cirrhosis, hepatocellular carcinoma) for future use. In the process, we wish to learn about the epidemiology of hepatitis C in

Prague and provide new data that may be ultimately used for designing better intervention strategies, including the identification of new antiviral drug targets and HCV vaccine candidates. We also believe that what we learn in Prague will have relevance to other regions in Central and Eastern Europe, including Russia where similar epidemics of IDU are occurring.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: HEPATITIS C VIRAL MUTANTS AND HUMAN T CELL FUNCTION**

  Principal Investigator & Institution: Wang, Huiru; Medicine; University of Illinois at Chicago 1737 West Polk Street Chicago, Il 60612

  Timing: Fiscal Year 2002; Project Start 01-JUN-2001; Project End 31-MAY-2004

  Summary: (adapted from the application) **Hepatitis C Virus** (HCV) persists in more than 80% of those initially infected and over the course of decades causes chronic liver disease that can be associated to hepatocellular carcinoma, cryoglobulinemia and autoimmunity. Immune responses to HCV have been studied at the antibody, CD4, and CD8 levels in both the peripheral blood and the liver. Strong antibody responses are observed to all HCV proteins and both helper and cytotoxic T-cells have been isolated from each site of infection. Despite such evidence of immune recognition, the mechanisms by which HCV establishes and maintains infection are not well understood. Speculation that chronic HCV infection may arise from several different mechanisms is based on a number of observations that include evidence of immune deviation and generation of escape variants, neither of which is mutually exclusive. Type 2 cytokines have been observed in the serum of chronically infected patients and studies with peripheral blood T-cells have shown that HCV antigen stimulation often results in secretion of Type 2 cytokines. Paradoxically, studies in the liver suggest that local production of Th1-associated cytokines correlates with progressive hepatic damage. Because of many such similar findings in a variety of models, responses in the peripheral blood are often discounted as irrelevant to site-specific immune responses. Recognizing that HCV also infects peripheral blood mononuclear cells, however, it may be possible to reconcile such disparate results if it is postulated that the peripheral blood provides a source for constant re-infection of the liver and thus also, chronic viral persistence. Therefore, an understanding of peripheral immune responses to HCV is also critical to understanding viral immunopathogenesis. Our hypothesis is that the evasive mechanisms used by HCV arise from intrinsic hypermutability in T-cell epitopes encoded throughout the genome and that under host immune selection, there is an accumulation of HCV quasispecies expressing functionally tolerogenic epitopes conducive to viral persistence. We further postulate that in the evolutionary process by which such functionally tolerogenic epitopes are selected, helper T-cell responses shift towards a Th2 phenotype favoring chronic infection and creating a tolerogenic bias that specifically dampens effective anti-HCV responses. We believe that understanding the structural constraints upon helper T-cell interactions with functionally distinct HCV epitopes provides a powerful vantage point from which to study immune regulation in humans, our primary interest, and also leads to strategies for intervening in the infectious process. Our aims are to examine the relationship between viral mutation and functionally distinct helper T-cell epitopes that stimulate production of different cytokines; to determine the mechanism of IL-2 suppression in response to an immunodominant epitope within the non-structural (NS) 3 protein antigen of HCV.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: HEPATITIS C VIRAL QUASISPECIES WITHIN THE LIVER**

  Principal Investigator & Institution: Di Bisceglie, Adrian M.; Professor of Internal Medicine; Internal Medicine; St. Louis University St. Louis, Mo 63103

  Timing: Fiscal Year 2002; Project Start 30-SEP-1999; Project End 31-AUG-2004

  Summary: This application proposes to examine the biological significance of liver-specific hepatitis C viral (HCV) quasispecies variants. HCV is a positive single-stranded blood-borne RNA virus which infects humans and may cause chronic liver injury including hepatitis, cirrhosis and hepatocellular carcinoma through chronic infection. The liver is the major site of replication of HCV although HCV RNA is also found in the blood of infected individuals. The genome of HCV varies considerably in nucleotide sequence from isolate to isolate, allowing HCV to be divided into genotypes and subtypes. However, multiple isolates from a single infected individual may also have considerable variability in nucleotide and amino acid sequence, particularly within the hypervariable region (HVR1) of the envelope gene. HRV1 is a sequence of approximately 27 amino acids at the likely N terminus of the HCV E2 glycoprotein. Variations in HRV1 provide markers for identification and tracing of HCV quasispecies variants. Quasispecies arise because of the high error frequency associated with viral RNA replication and immune pressure appears to be a factor in their selection. Preliminary experiments conducted by the applicants have shown that a greater number of HCV quasispecies variants are found within the liver compared to serum, even allowing for differences in viral load and that some liver-specific variants appear to be present. The applicants hypothesize that an excess of HCV quasispecies variants are continually being produced by errors in replication of HCV RNA within hepatocytes, some of which are cleared from serum by neutralizing antibodies, leaving behind in the circulation those variants which have escaped immune clearance. The significance of these differences will be examined through cloning and sequencing quasispecies variants present in both serum and liver. Changes in HCV quasispecies over time will be sought by comparing nucleotide sequence in HRV1 region before and after liver transplantation. The presence of possible neutralizing antibodies in serum directed against liver-specific quasispecies variants will be sought by enzyme-linked immunoassays based on peptides synthesized according to nucleotide sequences of the various cloned quasispecies. In addition, immunoreactivity to the whole of the E1 and E2 proteins cloned and expressed in mammalian cells will be determined. Differences in presence, titer and reactivity of antibodies against quasispecies will be compared to determine whether neutralizing antibodies account for clearance of some quasispecies from serum but not liver. These studies have great potential significance for understanding of viral clearance, development of persistent infection and for the development of a vaccine against HCV.

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- **Project Title: HEPATITIS C VIRUS COINFECTION IN HIV-1 INFECTED SUBJECTS**

  Principal Investigator & Institution: Rakela, Jorge L.; Chair; Mayo Clinic Coll of Med, Mayo Clinic Az Sc Johnson Research Medical Building Scottsdale, Az 85259

  Timing: Fiscal Year 2002; Project Start 30-SEP-2000; Project End 31-AUG-2004

  Summary: (Applicant's Abstract) **Hepatitis C virus** (HCV) coinfection is common in human immunodeficiency virus type I (HIV-1) infected subjects. Epidemiological data suggest that in HIV-1 and HCV coinfected patients, HCV infection is more severe and progression to AIDS is more rapid. Furthermore, HIV infection was reported to facilitate mother-to-infant transmission of HCV and also HCV infection was reported to facilitate

mother-to-infant transmission of HIV. Our overall hypothesis is that HCV replicates in lymphoid cells and that this phenomenon is responsible for the observed interactions between HIV-1 and HCV infections. Using strand-specific assays, we have demonstrated the presence of HCV RNA negative strand, which is a viral replicative intermediary, in multiple extrahepatic sites, but particularly common in lymphoid tissue. This infection was mainly localized in monocyte/macrophage cells. Moreover, we found that viral sequences at extrahepatic replication sites commonly differ from circulating and liver-derived sequences. Our proposal aims to further characterize extrahepatic HCV replication among HIV-1-infected subjects. Furthermore, we will analyze the presence of HCV replication in peripheral blood mononuclear cells (PBMCs) and cervical lavage cells in a large group of HIV-1-positive mothers and we will correlate these data with transmission of HCV and HIV-1 into children. To determine whether macrophage-derived HCV strains are responsible for viral transmission into children, we will analyze viral quasispecies composition in serum and PBMCs from mothers and children and in cervical lavage cells from mothers. We will also determine whether HCV infection of antigen presenting cells affects their function. Accordingly, we will culture dendritic cells from HCV-infected and uninfected individuals and compare them in functional assays in vitro. In summary, our studies will further characterize extrahepatic replication of HCV in HIV-1 infected subjects and will elucidate its role in mother-to-infant transmission of these two viruses.

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- **Project Title: HEPATITIS C VIRUS IMMUNOBIOLOGY AND PATHOGENESIS**

  Principal Investigator & Institution: Chisari, Francis V.; Professor & Head; Scripps Research Institute Tpc7 La Jolla, Ca 92037

  Timing: Fiscal Year 2003; Project Start 12-DEC-1997; Project End 31-MAY-2008

  Summary: (provided by applicant): The **hepatitis C virus** (HCV) is a plus-stranded RNA virus that infects more than 100 million people and causes acute and chronic hepatitis and hepatocellular carcinoma. The outcome of HCV infection is thought to be determined by the high replication and mutation rates of the virus, and by the kinetics, magnitude, quality and duration of the T cell response. In particular, many HCV-specific CD8(T cells that can be visualized with HLA class I tetramers fail to produce inteferon gamma (IFNgamma), especially during chronic infection. The potential importance of this dysfunctional phenotype in the pathogenesis of HCV infection is suggested by our recent observations that: (a) it also heralds the onset of the CD8(T cell response to HCV during the incubation phase of infection; (b) it correlates with high viral titers and significant liver cell injury during acute viral hepatitis; (c) it recovers or is replaced by CD8+ T cells that produce IFNgamma when the virus is cleared. We suggest that dynamic changes in T cell function such as this, and others that have not yet been examined, may have an important impact on the course and outcome of HCV infection. In the current application, therefore, we will test this hypothesis by comparing the phenotypic and functional evolution of the CD4(and CD8(T cell responses to HCV with the severity and duration of infection in acutely and chronically infected humans and chimpanzees. We will also perform in vivo depletion experiments to directly examine whether CD4+ or CD8+ T cells control HCV infection, and to determine the extent to which their antiviral potential is mediated by IFNgamma. This information will not only provide fundamental insight into the immunobiology of HCV infection, it may also lead to the development of immunotherapeutic and antiviral approaches to prevent and treat this serious disease.

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- **Project Title: HEPATITIS C VIRUS IN ETIOLOGY OF WA RHEUMATOID FACTORS**

  Principal Investigator & Institution: Agnello, Vincent; Lahey Clinic 41 Mall Rd Burlington, Ma 01805

  Timing: Fiscal Year 2001; Project Start 30-SEP-1999; Project End 31-AUG-2004

  Summary: We have established the association of **hepatitis C virus** (HCV) infection with type II cryoglobulinemia (MC-II) and with the WA crossidiotype (XId) positive monoclonal rheumatoid factors (WA mRF), and the selective concentration of HCV and very low density lipoprotein (VLDL) in these cryoglobulins. We have also established that the LDL receptor mediates endocytosis of HCV and other members of the Flaviviridae family and that the apolipoprotein E epsilon2 allele in HCV infected patients increases the risk of developing MC three-fold. The broad, long-term objective of this proposal is to investigate how WA mRF are produced in MC-II and how they may affect chronic HCV infection. Two hypotheses will be tested: 1) In patients with MC-II associated with HCV infection, the WA mRF is produced as a result of chronic stimulation of B cells by complexes of HCV and VLDL. It is postulated from this hypothesis that initially a WA+ RF- IgM is produced and that rheumatoid factor activity arises as a result of a point mutation in the CDR3 with chronic HCV infection. It will be determined whether: a) WA+ RF- IgM has antibody activity to HCV VLDL, b) WA mRFs ve cross reactivity with the same antigen, and c) cells producing WA mRF- IgM are the precursors of those producing WA mRF+ IgM. Lymphoid aggregates in liver biopsies from HCV infected patients with mixed cryglobulinemia will be examined for the presence of WA+ RF- and WA+ RF+ B cells and the results compared to DNA and mRNA analysis for WA sequences from the same liver biopsies and paired peripheral bloods. 2) LDL receptor endocytosis is a major route of HCV infection of hepatocytes. The main physiologic role of WA antibodies is to block endocytosis of HCV VLDL complexes by the LDL receptors. The retarded endocytosis of HCV-VLDL complexes containing apolipoprotein E2 via the LDL receptor is the mechanism underlying the apo E2 risk factor for developing MC-II. Flow cytometry, in situ hybridization, and quantitative PCR assays will be used to study the endocytosis of HCV-lipoprotein complexes to determine a) the rate of endocytosis of HCV-VLDL of various apo E phenotypes and various HCV genotypes and b) the effect of WA mRF and WA+ RF-IgM on the rates of endocytosis. In addition, the role of lipoprotein concentration, apo E phenotypes and HCV genotypes on the distribution of HCV among lipoproteins in HCV infected individuals with and without cryoglobulinemia and on the selective concentration on VLDL with HCV in MC-II will be determined. The proposed studies may provide insights into the etiology of MC-II, the mechanism of HCV infection, and the role of natural antibody systems in the immune response to HCV, and may lead to better therapy, early detection and prophylaxis of the disease.

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- **Project Title: HEPATITIS C VIRUS INDUCED IL-8 & INHIBITION OF INTERFERON**

  Principal Investigator & Institution: Polyak, Stephen J.; Assistant Professor, Research; Laboratory Medicine; University of Washington Grant & Contract Services Seattle, Wa 98105

  Timing: Fiscal Year 2003; Project Start 15-SEP-2003; Project End 31-AUG-2008

  Summary: (provided by applicant): **Hepatitis C virus** (HCV) infects an estimated 3% of the world's population, and is a significant cause of liver disease. The interactions that

occur between HCV proteins, cellular proteins and signal transduction machinery have a significant influence on virus replication, persistence, pathogenesis, and the outcome of antiviral therapy. Mutations in HCV proteins correlate with clinical responses to IFN therapy, and affect HCV replication in vivo and in vitro. HCV proteins also inhibit the antiviral actions of interferon (IFN). We have found that the HCV NS5A protein induces the pro-inflammatory CXC chemokine, interleukin 8 (IL-8), which is associated with inhibition of the IFN system. The in vivo significance of this finding is shown by elevated IL-8 levels in persons with chronic hepatitis C. In the HCV replicon system, we have also found that HCV replication is associated with increased production of IL-8 and attenuated IFN-induced transcriptional responses. Furthermore, exogenous IL-8 stimulates HCV protein production in HCV replicons. In this proposal, we hypothesize that HCV induced IL-8 inhibits the antiviral actions of IFN, promotes HCV replication, and contributes to HCV pathogenesis. To address this hypothesis, we propose 2 specific aims (SA) to determine the mechanisms of HCV induction of IL-8, and to determine the mechanisms of IL-8's anti-IFN activity. SA1 will focus on HCV induction of IL-8 via both transcriptional activation of the IL-8 promoter and stabilization of IL-8 mRNA. SA2 will focus on IL-8 mediated inhibition of the IFN-induced 2'-5' oligoadenylate synthetase/RNase L system, as well as cross-talk between IL-8 induced mitogen activated protein (MAP) kinases and IFN induced STAT-JAK pathways. The characterization of a new mechanism for modulation of the IFN system by a chemokine may be relevant to pathogenesis of chronic hepatitis C and many other viral and non-viral diseases. Moreover, IL-8 or its receptors may prove to be suitable targets for therapeutic intervention in chronic hepatitis C.

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- **Project Title: HEPATITIS C VIRUS NS5A PROTEIN AND LIPID DROPLETS**

  Principal Investigator & Institution: Yen, Tien-Sze Benedict.; Professor; Northern California Institute Res & Educ 4150 Clement Street (151-Nc) San Francisco, Ca 941211545

  Timing: Fiscal Year 2002; Project Start 29-SEP-2002; Project End 31-AUG-2005

  Summary: (provided by applicant): **Hepatitis C virus** (HCV) is a major cause of chronic hepatitis, cirrhosis, and hepatocellular carcinoma in the US and in many other parts of the world. Currently available therapy is not effective in many patients. Drug and alcohol abusers are especially at risk. A high percentage (up to -40%) of people with alcoholic liver disease show evidence of active infection by HCV. The prognosis for these people is significantly worse than for infected people without alcohol abuse, in that they show more hepatic dysfunction, increased hepatic pathology, and accelerated rates of liver fibrosis. Many studies also show increased levels of viral replication and hepatocellular carcinoma and lower response rate to therapeutic intervention. Therefore, there is an urgent need for novel drugs to block HCV replication in infected people who abuse alcohol. One approach to finding new drug targets is to look for specific virus-host interactions that are necessary for the viral life cycle. We are concentrating on the relationship between HCV proteins and lipid droplets, since hepatic steatosis is common in both alcoholic liver disease and chronic hepatitis C. HCV core protein is known to localize, in part, to the surface of lipid droplets. Another group has recently found that the NS5A protein is also localized to lipid droplets. This finding has been independently confirmed in our laboratory. We have also mapped a region of NS5A protein that can mediate the localization of heterelogous proteins to lipid droplets, and found a cellular lipid droplet protein that binds to this region of NS5A protein. The proposed experiments will test the hypothesis that this cellular protein mediates the localization of

NS5A protein to lipid droplets, and that the binding of NS5A protein to this protein and lipid droplets is necessary for high-level HCV RNA replication. We will also set up a rapid screening system to look for small molecules that can disrupt the interaction between NS5A protein and the cellular protein. It is anticipated that these interdisciplinary experiments will lead to the discovery of novel therapeutic agents for blocking HCV replication, especially for people with steatosis.

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- **Project Title: HEPATITIS C VIRUS NS5A PROTEIN AND OXIDATIVE STRESS**

  Principal Investigator & Institution: Siddiqui, Aleem A.; Professor; Microbiology; University of Colorado Hlth Sciences Ctr P.O. Box 6508, Grants and Contracts Aurora, Co 800450508

  Timing: Fiscal Year 2003; Project Start 08-JAN-2003; Project End 31-DEC-2007

  Summary: (provided by applicant): **Hepatitis C virus** (HCV) is one of the leading causative agents of chronic hepatitis and cirrhosis. HCV infection of liver is associated with the development of hepatocellular carcinoma. It is estimated that about 4 million people in the US are infected with HCV. The RNA genome of this virus encodes a polyprotein of 3010 amino acids. HCV RNA genome consists of unique sequences and structures at its 5' and 3' termini, which are essential features required for viral translation and replication. The RNA genome codes for three structural proteins and at least six nonstructural proteins. One of the nonstructural proteins, NS5A has generated significant levels of interest due largely to its suggested role in interferon-resistance. In this application, we propose to investigate the functions associated with the HCV NS5A. Translation and replication functions of the HCV RNA genome are associated with the ER membrane. These activities in the ER induce ER stress and ER overload responses. ER stress leads to unfolded protein response (UPR), which leads to activation of whole host of ER chaperone proteins. The ER overload response appears to involve two second messengers, calcium and reactive oxygen species. Their activities ultimately lead to the activation and translocation of transcription factors to the nucleus whereupon they bind cognate DNA sequences and regulate gene expression. NF-kappaB and STAT-3 are two such transcription factors which are activated by phosphorylation and are transported to nucleus. Herein, we propose to investigate the mechanism of activation of ER-nucleus signal transduction pathway by the HCV NS5A. These studies have the potential to provide information of direct relevance to the chronic liver disease pathogenesis including its progression to hepatocellular carcinoma associated with the HCV infection.

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- **Project Title: HEPATITIS C VIRUS NS5A PROTEIN AND PATHOGENESIS**

  Principal Investigator & Institution: Ray, Ratna B.; Pathology; St. Louis University St. Louis, Mo 63103

  Timing: Fiscal Year 2002; Project Start 15-FEB-1999; Project End 31-JAN-2004

  Summary: Hepatitis C virus (HCV) often causes a prolonged and persistent infection. Association between hepatocellular carcinoma (HCC) and HCV infection has been noted. Immune evasion and quasi-species nature are prominent features of HCV. Understanding the molecular basis of viral pathogenesis is a major challenge to gain insight into HCV associated disease progression. The pathogenesis of liver damage is likely to be related to both viral and immune mediated factors. Recent experimental evidence using HCV cloned genomic regions suggests that the NS5A protein has many intriguing properties. These include the presence of an interferon sensitivity

determining region (ISDR), direct repression of PKR, a regulatory role on important cellular promoters, and promotion of cellular transformation. Together these observations provide a compelling reason to focus and design studies to further our understanding of the molecular mechanism and cellular targets of HCV NS5A protein mediated biological functions. Available information suggests that during persistent infection NS5A protein may play a critical role in concert with cellular factors for virus mediated pathogenesis. This research proposal is designed to (1) Determine the role of HCV NS5A protein on cell cycle regulatory genes and map the transregulatory domain; (2) Investigation the interaction of HCV NS5A protein with cellular target protein(s); (3) Determine the role of HCV NS5A protein in cytokine mediated apoptosis; (4) Determine the transforming potential of HCV NS5A protein in primary human hepatocytes; and (5) Determine whether HCV NS5A protein expression promotes liver pathogenesis in transgenic mice. Results from this study will lead to a better understanding of the virus mediated pathogenesis. The long term goal of this study is to design effective strategies for the intervention of HCV mediated disease in humans.

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- **Project Title: HEPATITIS C VIRUS, ALCOHOL AND HOST DEFENSE**

  Principal Investigator & Institution: Szabo, Gyongyi; Professor; Medicine; Univ of Massachusetts Med Sch Worcester Office of Research Funding Worcester, Ma 01655

  Timing: Fiscal Year 2003; Project Start 15-SEP-2003; Project End 31-AUG-2008

  Summary: (provided by applicant): Alcohol use accelerates the progression of liver disease in chronic hepatitis C (HCV) infection; however, the interactions between alcohol and HCV have not yet been explored. Chronic HCV infection is associated with reduced HCV-specific immune responses, and alcohol use suppresses antigen-specific T cell activation via inhibition of monocyte and dendritic cell (DC) antigen presentation. Both chronic alcohol consumption and chronic HCV infection are independently associated with activation of inflammatory pathways that mediate hepatocellular injury. Thus, we hypothesize that alcohol, HCV interacts to activate non-specific pro-inflammatory cascades in chronic HCV infection, and this process may contribute to progression of liver damage. Based on our preliminary results, we propose that the pattern recognition receptor, toll-like receptor 2 (TLR2), mediates cellular activation by HCV core and NS3 proteins. We further postulate that alcohol may increase inflammatory cell activation by interacting with TLR2-mediated pathways. Our preliminary results show that myeloid DC (dendritic cells), the most potent antigen presenting cell type, have reduced T-cell activation capacity in patients with chronic HCV infection and this can be further decreased by alcohol treatment of DCs. Thus, we propose that alcohol contributes to the persistence of chronic infection in HCV by inhibiting functional maturation of dendritic cells, thereby decreasing antigen-specific T cell activation and viral recognition. The Specific Aims of this proposal are: 1. To investigate interactions between HCV- and alcohol-induced inflammatory pathways at the protein and mRNA levels and on activation of the nuclear regulatory kB/Rel pathway in normal monocytes and in patients with chronic HCV infection with and without alcohol use or chronic in vitro alcohol treatment. 2. To investigate the pattern recognition receptor, TLR2, as a putative receptor in cell activation by HCV proteins. This will be accomplished by testing cellular activation by HCV proteins in TLR2-transfected CHO and HEK cells and in macrophages of TLR2-deficient mice. The cooperation of TLR2 with other components of the TLR2 receptor complex required for successful transmission of HCV core and NS3 mediated cell activation will be identified by selectively investigating the roles of CD14, TLR 1, and TLR6. 3. To evaluate the

interactions between alcohol and HCV proteins on TLR2-mediated cell activation pathways by determining the effects of acute and chronic alcohol treatment on TLR2 expression, gene activation, and TLR2-mediated monocyte activation from normal controls and chronic HCV infected patients. Investigation of downstream elements involved in TLR2-mediated intracellular signaling after stimulation with core and NS3 proteins and their modulation by alcohol will be tested. 4. To delineate the role of TLR2-mediated signaling by HCV core and NS3 proteins in the reduced dendritic cell differentiation in HCV infected patients and to evaluate the effect of alcohol on TLR2-mediated signals in DC development. Results from these studies should reveal molecular and cellular mechanisms by which alcohol interacts with HCV infection to accelerate disease persistence and progression.

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- **Project Title: HEPATITIS VIRUS, ALCOHOL EXPOSURE AND OXIDATIVE STRESS**

  Principal Investigator & Institution: Hassan, Manal M.; Gastrointestinal Med Oncology; University of Texas Md Anderson Can Ctr Cancer Center Houston, Tx 77030

  Timing: Fiscal Year 2002; Project Start 30-SEP-2001; Project End 31-AUG-2004

  Summary: (provided by applicant) **Hepatitis C virus** (HCV) infection and alcohol abuse are the 2 major risk factors for hepatocellular carcinoma (HCC) in this country. The higher prevalence of HCV infection in the general population has resulted in a significant increase of the incidence of HCC in the United States. Although both HCV and alcohol can independently induce liver disease, exposure to both agents may accelerate the course of liver pathology and/or lead to more severe injury. The mechanism underlying the synergistic effect of HCV and alcohol intake is not well understood. One hypothesis is that both HCV and alcohol intake may contribute to chronic hepatitis, cirrhosis and subsequent liver cancer through enhanced oxidative stress. It is known that alcohol could induce oxidative stress and lipid peroxidation. Interestingly, a recent study has reported that HCV encodes a selenium (Se)-dependent antioxidant enzyme, glutathione peroxidase, GPx, and GPx may have a regulatory role in HCV replication. The virus-induced overexpression of GPx may lead to a decreased level of Se in the host due to the competition of HCV for Se. In fact, patients with HCV have been shown to have a significant decline in their serum Se. On the other hand, the hepatotoxicity of ethanol and its associated malnutrition will further reduce the cellular Se level. This additive decline in the Se level will make the cell more susceptible to reactive oxygen species (ROS). Previous studies have shown an association between oxidative DNA damage and either alcohol exposure or chronic viral infection. It seems that chronic HCV infection may lead to an increased ROS, overexpression of GPx and reduced serum level of Se. When the Se-GPx level is low, the virus will be more provoked for replication, leading to a higher viral load in the infected cell. Eighty newly-diagnosed HCC patients will be recruited from University of Texas MD Anderson Cancer Center (UTMDACC). The current project will explore the effect of dietary selenium intake and its interaction with HCV and alcohol intake in HCC in a case-control study. Eighty healthy individuals (first control group), matched with cases by age, sex and ethnicity, will be recruited from the patients non-blood relatives and friends from UTMDACC. To have a control group with comparable prevalence of HCV infection, 80 patients with liver cirrhosis, who have no evidence of HCC (second control group), will be recruited from Baylor College of Medicine. Information on alcohol intake, dietary Se intake and other risk factors will be collected by a questionnaire. The frequency and profile of hepatitis B virus (HBV) and HCV infection will be determined

by measuring serum HBsAg, anti-HBC, anti-HCV, and HCV-RNA. Oxidative stress will be evaluated by measuring the levels of serum Se, GPx activity, lipid peroxides, and 8-hydroxy-deoxyguanosine (8-OH-dG), a marker of oxidative DNA damage. The expression of GPx and the level of 8-OH-dG will also be measured in tissue samples from cirrhotic and HCC patients. Serum Se, GPx activity, lipid peroxides and oxidative DNA damage will be measured in relation to HCV and alcohol intake history.

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- **Project Title: HIV HCV COINFECTION--ANTIVIRAL THERAPY AND FIBROSIS**

  Principal Investigator & Institution: Thomas, David L.; Professor of Medicine; Medicine; Johns Hopkins University 3400 N Charles St Baltimore, Md 21218

  Timing: Fiscal Year 2002; Project Start 20-SEP-2000; Project End 31-JUL-2005

  Summary: (Applicant's Abstract) **Hepatitis C virus** (HCV) and human immunodeficiency virus (HIV) infections occur with alarming frequency in persons who misuse alcohol and illicit drugs. In East Baltimore, 80 percent of HIV-infected injection drug users also have HCV infection and one-half acknowledges regular, heavy alcohol use. This disease cluster may cause cirrhosis since HIV infection and heavy alcohol use are the two conditions that accelerate progression of hepatitis C. Recently the significance of these cofactors has been magnified by improved anti-retroviral treatments that dramatically reduce other opportunistic infections but may themselves cause liver toxicity. Accordingly, the 1999 US Public Health Service guidelines for management of HIV opportunistic infections considered hepatitis C but withheld recommendations for medical management because of the paucity of supporting data. In this investigation, we hypothesize that treatment of HIV and HCV infections will reduce progression of liver disease, after controlling for alcohol use. To test the hypothesis, we will first examine the success of prior anti-retroviral use with respect to liver fibrosis and then the change in fibrosis over three years of anti-retroviral experience. In addition, we will examine the effect of alfa-interferon based treatment for HCV infection with respect to fibrosis changes and eradication of HCV. Innovative tools will be tested to assess liver fibrosis (morphometrics), predict liver fibrosis (markers), and measure use of alcohol and medical adherence (A-CASI). Given the experience of the investigative team and the extensive preliminary data, we anticipate providing data that will directly affect forthcoming guidelines for the medical management of HIV-HCV coinfected persons.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: HIV TREATMENT IN THE HOMELESS: A PROSPECTIVE STUDY**

  Principal Investigator & Institution: Bangsberg, David R.; Assistant Professor; Medicine; University of California San Francisco 500 Parnassus Ave San Francisco, Ca 941222747

  Timing: Fiscal Year 2003; Project Start 01-JUL-1995; Project End 31-JAN-2005

  Summary: This is a proposal to continue and extend the longitudinal studies of HIV therapy, adherence to therapy and drug resistance in the REACH cohort of HIV-positive homeless and marginally housed persons. The cohort will be augmented by a third wave of sampling in the study population, all subjects will be followed for three years, and subjects on Highly Active Therapy (HAART) will be followed monthly with intensive measurement of adherence levels and monthly plasma storage for genotyping. The specific aims of the proposed research are: 1. Once-a-day therapy. To study the penetration and impact of once-a- day HAART in the REACH cohort, including its effects on adherence to therapy and the development of resistance. 2. Biology of

incomplete adherence. To divide subjects by adherence level and test four hypotheses on the biology of incomplete adherence to therapy, including hypotheses on the relationship between adherence level and viral fitness and the relationship between adherence level and immune response to therapy. These studies are collaborative with Drs M. McCune, S. Deeks, and R. Grant at UCSF. 3. Mortality and progression to AIDS, the effect of adherence to therapy on mortality and progression to AIDS, and the changing population prevalence of anti-retroviral resistance. 4. **Hepatitis C Virus** (HCV) co-infection. To study the penetration of and adherence to HCV therapy in the homeless and the effect of HCV co- infection on progression of HIV infection and mortality. The REACH cohort is the only representative cohort of HIV-positive persons recruited from the urban indigent, an increasingly important reservoir of HIV infection in the United States. This population is at high risk for adherence and the development of drug resistance. The proposed research will assist in the development of both behavioral and therapeutic strategies to extend treatment and reduce the risk of drug resistance in this important population.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: HIV/HCV CO-INFECTION: HAART AND CVD PATHOPHYSIOLOGY**

  Principal Investigator & Institution: Hurwitz, Barry E.; Professor; Psychology; University of Miami Coral Gables Box 248293 Coral Gables, Fl 33134

  Timing: Fiscal Year 2002; Project Start 30-SEP-2002; Project End 31-AUG-2007

  Summary: (provided by applicant): HAART medication has been implicated as a potential etiopathological source of the increased prevalence of cardiovascular disease (CVD) risk in HIV infected persons. Although recent reports indicate an increasing rate of **Hepatitis C virus** (HCV) coinfection in the HIV-infected, and HCV infection independently communicates increased cardiovascular risk, the literature has not adequately assessed the possible role of HCV coinfection in cardiovascular pathogenesis in HIV spectrum disease. Comorbid conditions known as dysmetabolic syndrome X are independently associated with both HIV and HCV infection; the syndrome includes alterations in fat deposition, cardiac structure and function, and vascular endothelial function, as well as dyslipidemia and insulin resistance. Two pathophysiological sources in HIV and HCV infected persons is increased pathogen burden and diminished infection surveillance, which result in an elevation of proinflammatory processes. These processes have been shown to induce greater reactive oxygen species formation, which has been linked to atherogenesis and alterations in cardiac and vascular structure and function. Oxidative stress has also been associated with insulin resistance. Because of the possible role of HCV infection and HAART medication in cardiovascular disease risk and because proinflammatory and oxidative factors are likely mediators of this risk, the primary objective of the proposed study is to systematically examine these factors in 420 (of 465 screened) men and women, as a function of HIV and HCV infection, and coinfection. The influence of HAART treatment regimen (anti-retrovirals plus protease inhibitors [PI+] vs. anti-retrovirals without protease inhibitors [PI-]) on these outcomes will be assessed by nesting HAART regimen within the HIV+ groups, thereby yielding a six group comparison (HIV+PI+/HCV+ vs. HIV+PI-/HCV+ vs. HIV+PI+/HCV- vs. HIV+PI-/HCV- vs. HIV-/HCV+ vs. HIV-/HCV-). The secondary objective is to determine whether the data collected is described by the proposed pathophysiological model, which postulates that the burden of exposure to multiple infectious sources is associated with greater levels of proinflammatory factors and oxidative stress, and consequently greater CVD risk and diminished cardiovascular function.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: HIV-INFECTED PATIENTS' EXPERIENCES WITH HCV TREATMENT**

  Principal Investigator & Institution: Bova, Carol A.; None; Univ of Massachusetts Med Sch Worcester Office of Research Funding Worcester, Ma 01655

  Timing: Fiscal Year 2003; Project Start 01-JAN-2003; Project End 31-DEC-2004

  Summary: (provided by applicant): Chronic **hepatitis C virus** (HCV) infection affects 40,000 HIV positive patients in the United States. HCV treatment is associated with life-threatening side effects and antiretroviral drug interactions. Without treatment, increasing numbers of HIV positive patients will either die from end stage liver disease or from HIV-related complications because of the inability to use antiretroviral agents due to their hepatotoxicity. Data are limited, but the clinical impression is that this population less often accepts or completes HCV treatment. More information is needed about the experience of HIV-infected patients as they manage the process of HCV treatment. The purpose of this qualitative, longitudinal study is to develop a clear understanding of HIV-infected patients' experiences with HCV treatment. This understanding will improve our ability to design clinical interventions that support HCV treatment efforts in co-infected patients. The specific aims of this study are to (1) describe the subjective experiences of HIV-infected patients as they manage the process of HCV treatment, (2) examine the influence of health related quality of life, symptom experience, mental illness, substance abuse and the role of health care providers on the experience of HCV treatment in co-infected patients, and (3) explore the association between demographic, clinical cofactors and the HCV treatment experience. In-depth qualitative interviews will be conducted with 40 HCV/HIV co-infected patients at three time points (before treatment, 8-12 weeks into treatment and at treatment completion). Subjects who choose not to be treated will be interviewed also. The constant comparative method of content analysis will be used to abstract interview data on the HCV treatment experience. A meta-matrix will be used to integrate the qualitative, demographic and clinical cofactor data (HCV treatment adherence, HIV RNA, HCV RNA, HCV genotype, liver pathology, complete blood counts, liver function tests, HIV illness stage and co-treatment with antiretroviral agents). The proposed study is an essential step towards developing the foundation for clinical trials that test HCV treatment interventions among HIV-infected patients. Results of this study will also be valuable to clinicians, educators, researchers and those who develop treatment guidelines for HCV/HIV co-infected patients.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: HUMAN/PIG MODEL OF HEPATITIS C VIRUS FOR NEW VACCINES**

  Principal Investigator & Institution: Beschorner, William E.; Chief Scientific Officer; Ximerex, Inc. Omaha, Ne 681162461

  Timing: Fiscal Year 2004; Project Start 01-JUN-2004; Project End 31-MAY-2006

  Summary: (provided by applicant): **Hepatitis C virus** (HCV) has emerged as a major public health problem. World wide, as many as 200 million people are infected. In the United States, an estimated 3.9 million are infected, with 2.7 million Americans chronically infected. The immune response of the patient determines if the patient is cured of the virus, develops a lifelong infection, or develops severe liver disease. Progress in the treatment and prevention of HCV is severely hampered by the lack of a suitable animal model. Chimpanzees are the only animals other than humans that are infected with HCV. The pathogenesis differs from human hepatitis, however. Furthermore, the ethics and availability of chimpanzees limits the studies that can be

done. A promising model was recently developed by engrafting human hepatocytes in immune deficient mice. This model, however, cannot assess the immune response to the virus or vaccines. We have developed technology for engrafting human liver cells in immune competent pigs. The innovations include transplanting cells into fetal pigs in utero and the development of unique transgenic pigs that enhance the growth of human liver cells. This study will inoculate HCV into hybrid swine with human liver cells and evaluate the virus proliferation, monitor the persistence of the virus and liver disease, and characterize the immune response. A large animal immune compentent model of HCV will lead to a better understanding of the pathogenesis of **hepatitis C virus** and to more effective vaccines and immune therapy.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: HUMORAL IMMUNE RESPONSE IN HEPATITIS C**

  Principal Investigator & Institution: Foung, Steven K.; Associate Professor; Pathology; Stanford University Stanford, Ca 94305

  Timing: Fiscal Year 2002; Project Start 15-JUL-2001; Project End 31-MAY-2006

  Summary: (provided by applicant): Evidence for a human humoral immune response to HCV infection providing at least partial protection is accumulating. The observation that antibodies induced to a hypervariable region on HCV E2 envelope protein designated HVR1 have in vitro and in vivo virus neutralization activity indicates that protective antibodies can be elicited. However, antibodies to HVR1 are highly restrictive and are a contributing factor in the development of escape mutants. The primary goal of this project is to develop potent neutralizing human monoclonal antibodies (HMAbs) that could ultimately be used in immunoprophylaxis and potentially for the treatment of HCV infection. We hypothesize that the majority of antibodies with the broadest and most potent activities will recognize conformational epitopes. Preliminary studies indicate that selected individuals with HCV genotype 2a infection are more likely to mount a protective antibody response. It is the intent of this project to focus on the production of HCV-HMAbs to E2 from these selected individuals. More importantly, the recent development of a small animal model for acute HCV infection will permit an eff aboutcient means to test for virus neutralization. A unique irnmunocompromised mouse has been developed capable of sustaining human liver tissues infected with HCV under the renal capsule for up to 26 days. During this period, viral replication occurs as measured by increasing serum viral load. Preliminary studies with three HCV-HMAbs (of which 2 are to conformational epitopes on HCV E2) injected by intraperitoneal route 17-20 days post-transplant of infected tissues significantly reduced HCV viral load in a dose-dependent manner. The aims of the proposal are to generate HMAbs to HCV E2 protein from peripheral B-cells of individuals infected with genotype 2a; test selected antibodies in a novel human-mouse chimera small animal model for in vivo protection; and determine the breadth of reactivity of these antibodies to divergent HCV isolates.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: IDENTIFYING DETERMINANTS OF HCV TROPISM**

  Principal Investigator & Institution: Dragic, Tatjana; Assistant Professor; Microbiology and Immunology; Yeshiva University 500 W 185Th St New York, Ny 10033

  Timing: Fiscal Year 2003; Project Start 30-SEP-2003; Project End 31-MAR-2008

  Summary: (provided by applicant): It is estimated that 170 million people worldwide are infected with the **Hepatitis C virus** (HCV) and are at risk of developing chronic hepatitis or cirrhosis, the latter often leading to hepatocellular carcinoma. There is

currently no vaccine and licensed therapies are associated with modest efficacies and significant toxicities. Despite the urgency of this worldwide public health problem, our basic understanding of HCV replication and pathogenesis remains poor due to a lack of key experimental models. For example, difficulties in culturing the virus in vitro and expressing native, fusogenic envelope glycoproteins have greatly limited studies of HCV tropism and entry. These are critical aspects of viral biology because the host range and pathogenesis of enveloped virus infection is largely determined by the selective interaction of viral envelope glycoproteins with cell-surface receptors. A major goal in HCV research is to understand how HCV targets the liver and by what mechanism it enters host cells. Recently, a major breakthrough in the field has been the development of retroviruses pseudotyped with HCV envelope glycoproteins that specifically mediate infection of primary hepatocytes, as well as certain other human cells. We will use this new experimental system to study HCV entry into target cells. Alterations in naturally occurring HCV envelope glycoproteins may predicate differences in receptor usage and target cell tropism in vivo. To investigate the range of HCV cellular tropism, pseudotypes incorporating envelope glycoproteins from clinical HCV isolates will be tested for their ability to enter relevant primary cells and cell lines. A functional cDNA cloning approach will be used to identify cell-surface receptors that specifically mediate HCV entry into different target cells. However, these receptors may be ubiquitously expressed and HCV targeting to different cell types may be determined by another mechanism. We recently demonstrated that L-SIGN and DC-SIGN are specific HCV-capture receptors and we will explore whether they mediate infection of target cells in trans, thereby determining HCV tropism. The major objective of our work is to identify the basic protein interactions that mediate HCV tropism, which will serve as a foundation for detailed structure/function analyses of HCV receptors and envelope glycoproteins.

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- **Project Title: IMMUNE COMPLEXES: ORIGINS AND EFFECTS IN HCV INFECTION**

  Principal Investigator & Institution: Dustin, Lynn B.; Assistant Professor; Lab/Virology & Infect Diseases; Rockefeller University New York, Ny 100216399

  Timing: Fiscal Year 2003; Project Start 30-SEP-2003; Project End 31-JAN-2008

  Summary: (provided by applicant): A substantial fraction of those infected with the **hepatitis C virus** (HCV) have immune complexes in the serum. These may be asymptomatic, or they may cause symptoms of mixed cryoglobulinemia. We have found that many HCV patients have a significant increase in the frequency of circulating B cells. These cells were not increased as a result of activation, since HCV patients had an increase in B cells of a resting, naive phenotype. Almost all HCV patients studied had increased numbers of B cells that resemble transitional cells recently released from the bone marrow. We have also found that approximately half of the patients studied have immune complexes directly associated with peripheral blood B cells, suggesting that some immune complexes may be overlooked in screens of serum. Immune complexes were found independently of B cell frequency. The long-term goal of this proposal is to understand why immune complexes are produced in HCV patients, and how these complexes affect viral binding and tropism. We will isolate immune complexes from the serum as well as from the B cell surface. Using quantitative PCR methods, we will determine what fraction of the virus in the blood is actually associated with immune complexes in the serum and on cells. Using a novel pseudotype assay for viral attachment and entry, we will test the hypothesis that immune complexes facilitate viral

entry into target cells or the transfer of virus from one cell type to another. In addition, we will evaluate the role of chemokines found in the blood during HCV infection, in the accumulation of B cells with a native or T1/T2 transitional phenotype in HCV patients. A mouse model will be developed to study the effects of overproduction of specific chemokines in the liver, on the frequency and phenotype of circulating B cells. This may improve our understanding of the genesis of lymphoid malignancy in HCV patients. These studies will improve our understanding of the origins of cryoglobulinemia, a significant extra hepatic manifestation of HCV infection. By characterizing the roles of immune complexes in cell entry, these studies may also lead to a better understanding of HCV pathogenesis and improved design of therapeutic and preventive vaccines.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: IMMUNE RESPONSES IN ACUTE HEPATITIS C INFECTION**

  Principal Investigator & Institution: Rosen, Hugo R.; Associate Professor; Medicine; Oregon Health & Science University Portland, or 972393098

  Timing: Fiscal Year 2002; Project Start 15-SEP-2002; Project End 31-MAY-2006

  Summary: (provided by applicant): Approximately 2 percent of the U.S. population has HCV antibodies, and it is estimated that 10,000 people die annually of HCV-related complications including liver failure or cancer. Although new therapies have improved the rates of sustained response, the majority of patients are nonresponders to antiviral treatment, remaining at risk for disease progression. Although chronic HCV infection is very common, it is rarely identified acutely, and patients rarely seek medical attention until long after chronic infection is established. The very nature of this infection has made it extraordinarily difficult to study the early disease course except in the subset of individuals with definitive early symptoms and diagnosis. In this proposal we will direct our studies to the analyses of the specific cellular immune response to **hepatitis C virus** (HCV) infection as it occurs very early following acute infection in a community-based cohort we have identified. The recent development of immunologic techniques that directly quantitate virus-specific lymphocytes ex-vivo will enable us to study the interactive mechanisms among virus, clinical disease, and host immune responses from the incubation phase. Detailed information of this stage of infection is clearly of value both in understanding the pathogenesis of the disease and potentially vaccine design. Our goal is to elucidate the cellular immune and virologic events in the initial stages of HCV infection that are likely to be crucial in determining self-limited infection versus chronic viral persistence and progressive liver injury. The specific aims outlined in this proposal include: To precisely examine the magnitude, kinetics, and breadth of HLA class I- and II- restricted cellular immune responses directed specifically against HCV and assess how these responses correlate with recovery versus chronic evolution; to characterize the temporal relationships between the level of HCV replication, its genetic diversity and the subsequent cellular immune response elicited by the viral infection. We propose to define how the host immune response shapes the kinetics of HCV replication. Furthermore, we anticipate that a subset of individuals who initially showed vigorous CD8+ T cell responses and control of viral replication will demonstrate abrogated HCV-specific immune responses over time and this will be associated with a rebound in circulating HCV viremia. In this subset of individuals, we propose to examine whether viral mutational events (yielding a high ratio of amino acid-changing substitutions to antigenically silent nucleotide base changes) in CD8+ T cell epitopes in viva has led to the generation of variant peptides that are no longer recognized by T cells.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: IMMUNOGENICITY OF HEPATITIS C VIRUS (HCV) LIKE PARTICLES**

  Principal Investigator & Institution: Barber, Glen N.; Professor; Microbiology and Immunology; University of Miami-Medical Box 248293 Coral Gables, Fl 33124

  Timing: Fiscal Year 2003; Project Start 01-AUG-2003; Project End 31-JAN-2008

  Summary: (provided by applicant): **Hepatitis C virus** [HCV], a member of the Flaviviridae, is a major cause of chronic hepatitis, liver cirrhosis and hepatocellular carcinoma. Acute infection with HCV is associated with persistent viral replication in approximately 80-90% of cases, with an estimated 200 million people infected worldwide. Presently, the only effective therapy against HCV infection is type I interferon [IFN] currently in combination with the nucleoside analogue ribavirin. However, response rates vary from 5% to 50%, depending on race and gender, thus leaving many infected individuals untreatable. Presently, there is no vaccine for HCV and therefore a collective need to develop preventive strategies as well as new therapies. The search for effective vaccines is hampered, however, by the inability to grow candidate HCV vaccine preparations in vitro and by the prevalence of numerous HCV quasispecies that have evolved due to the virus lacking a proof reading mechanism while replicating. Since HCV cannot be efficiently manufactured for vaccine assessment, we have synthesized, in mammalian cells, highly immunogenic, non-infectious HCV-like particles comprised of the core, E1 and E2 products of HCV. This was achieved by cloning the core/El/E2 genomic region of HCV into the relatively simple, nonpathogenic negative-stranded virus, vesicular stomatitis virus (VSV). Following infection of tissue cultured mammalian cells with VSV/HCV recombinant viruses, high levels of authentic core/El/E2 HCV proteins were generated that autoassembled into HCV-virus-like particles (VLPs). Importantly, our preliminary data further indicates that VSV/HCV induced cell-mediated and humoral activity to all the structural proteins in immunized mice. Thus, our HCV expression system may have the capacity to generate effective, multivalent immune respones to a variety of HCV encoded proteins. Given this data, we aim to analyze the potency of the rVSVs system that expresses HCV gene products or purified HCV-like particles themselves, in vaccine studies designed to further evaluate whether robust cell-mediated and humoral responses can be safely and effectively obtained to multiple HCV epitopes.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: IMMUNOREGULATORY EFFECTS OF MUTATION IN HCV NS3 ANTIGEN**

  Principal Investigator & Institution: Eckels, David D.; Senior Investigator; Blood Center of Southeastern Wisconsin Milwaukee, Wi 532012178

  Timing: Fiscal Year 2002; Project Start 15-MAR-2001; Project End 31-MAR-2002

  Summary: Hepatitis C Virus (HCV) is an enigma because it is recognized by both the cellular and humoral compartments of the immune system, yet it persists in at least 85% of those infected. Clearly, there must exist an immune deregulation of the response to HCV. We think that under host immune selection, there is an accumulation of HCV quasi species expressing functionally tolergenic epitopes conducive to viral persistence. We further postulate that as apart of the evolutionary process by which such functionally tolergenic epitopes are selected, helper T-cell responses shift towards a Th2 phenotype favoring chronic infection and creating a tolerogenic bias that specifically dampers effective anti-HCV responded even to wild-type virus. The aims of this proposal are: 1) to establish a frequency hierarchy for clones recognizing Th1 epitopes in

the NS3 antigen, a protein critical to HCV infection and replication. 2) to determine the mechanism of IL-2 suppression in response to an immunodominant epitope within the nine-structural (NS) 3 protein antigen of HCV. 3) to examine the relationship between viral nutation and functionally distinct helper T-cell epitopes that stimulate production of different cytokines. 4) to define the location and cytokine profiles of functionally distinct epitopes found in the nucleocapsid or Core protein antigen of HCV. We believe that understanding the structural constraints upon helper T-cell interactions with functionally distinct HCV epitopes provides a powerful vantage point from which to study immune regulation in humans and may lead to strategies for interviewing in the infectious process. Our studies are designed to test some of the in vitro correlates of this hypothesis and to gain insights into how natural variations in viral epitopes can lead to modulation of human T-cell responses. An understanding of this process is likely to bear on mechanisms and consequences of immune recognition as well as avenues of anti-viral therapeutic intervention. As we strive to address a number of important questions concerning HCV mutation and its effects on immune function, we postulate that this probably involves division of immune responses towards a Th2 or tolerogenic phenotype.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: IMPACT OF HCV NS3/4A PROTEASE ON HOST INNATE IMMUNITY**

  Principal Investigator & Institution: Li, Kui; Microbiology and Immunology; University of Texas Medical Br Galveston 301 University Blvd Galveston, Tx 77555

  Timing: Fiscal Year 2003; Project Start 01-SEP-2003; Project End 31-AUG-2005

  Summary: (provided by applicant): The mechanisms underlying the persistence of HCV infection are poorly understood. HCV E2 and NS5A have been suggested to inhibit cellular antiviral responses; however, data have been controversial. In collaboration with Dr. Michael Gale's group, we recently demonstrated that the NS3/4A serine protease blocks virus-induced phosphorylation and activation of interferon regulatory factor 3 (IRF-3), a key transcriptional factor in initiating cellular antiviral responses. However, the detailed consequences of this blockade, i.e. the alterations of downstream hepatocellular antiviral defensive gene expression, which may contribute to the persistence of hepatitis C, remain to be completely elucidated. In addition, the mechanisms by which NS3/4A protease blocks IRF-3 phosphorylation are yet not known. The primary goal of this proposal is to explore the answers of these issues using the recently-developed functional genomics approaches including microarrays and proteomics. Specific Aim 1, to identify and profile IRF-3 dependent and independent antiviral response genes of hepatocytes that are blocked /suppressed by NS3/4A expression or by genome-length HCV RNA replication. Cells that (1) conditionally express the NS3/4A protease, (2) contain replicating full-length HCV RNA, or (3) conditionally express a dominant negative IRF-3 mutant will be challenged with Sendai virus (SenV), and differences in SenV-activated gene expression will be identified using Affymetrix microarrays and compared with those from clonally matched HCV-negative cells. These experiments should identify antiviral genes downstream of the IRF-3 pathway and other possible pathways that are blocked/suppressed by NS3/4A protease. They will also provide information on whether other HCV proteins and IRF-3 independent pathways contribute to the persistence of HCV infection. Specific Aim 2, to explore the cellular changes at protein level by which NS3/4A protease blocks IRF-3 phosphorylation using a proteomics approach. Cells that conditionally express the NS3/4A protease will be challenged with SenV, and differences in protein expression

before and after challenge, in the presence and absence of NS3/4A will be identified by two-dimensional gel eletrophoresis coupled with automated polypeptide sampling and polypeptide sequencing by mass spectrometry. This approach is likely to identify the virus-activated kinase (VAK) or other signaling components indispensable for virus-induced IRF-3 phosphorylation that are inhibited by the NS3/4A serine protease. This proposal should lead to a better understanding of the mechanisms how HCV disrupts the innate immunity and causes persistent infection in hepatocytes.

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- **Project Title: IMPROVED CELL CULTURE SYSTEMS FOR HEPATITIS C VIRUS**

  Principal Investigator & Institution: Hicks, James; Virogenomics, Inc. 9020 Sw Washington Square Rd, Ste 140 Tigard, or 972234433

  Timing: Fiscal Year 2002; Project Start 01-JUN-2002; Project End 31-MAY-2003

  Summary: (provided by applicant): **Hepatitis C virus** is rapidly becoming one of the most important infectious health problems and is approaching epidemic status world wide. The CDC estimates that HCV may have already infected more that three million people in the US alone. Treatments for the chronic liver disease that eventually occurs years after HCV infection are limited to interferon and a few experimental antiviral compounds. One of the biggest obstacles to finding new drugs is the lack of a useful culture system for the virus. Dr. Jay Nelson and co-workers have discovered and cultured several new types of human cells that are apparently more permissive for viral replication. Virogenomics has been testing these cells for their ability to support infection and repliction HCV with some encouraging results. The aim of this Phase I project is confirm replication of HCV in activated macrophages or transformed hepatic endothelial cells in culture using a very sensitive TaqMan assay to verify replication by detecting production negative strand RNA. Success in the Phase I part of the project will lead to extended Phase II goals that will aim to create a robust culture system suitable fordrug screening, and look for alterations in gene expression caused by HCV infection through microarray analysis that could yield new host gene targets for blocking the pathogenic effects of the virus.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: INCIDENT HIV INFECTION AND IMMUNE RESPONSE TO HCV**

  Principal Investigator & Institution: Cox, Andrea L.; Medicine; Johns Hopkins University 3400 N Charles St Baltimore, Md 21218

  Timing: Fiscal Year 2003; Project Start 01-JUL-2003; Project End 31-MAY-2008

  Summary: (provided by applicant): Dr. Cox is an infectious disease fellow at the Johns Hopkins University (JHU) and has spent the last two years working with her mentors, Drs Thomas, Ray, and Pardoll on the cellular and humoral immune responses to **hepatitis C virus** (HCV) infection. Through this award, Dr. Cox hopes to conduct basic science research on HCV immunology as a faculty member in the Division of Infectious Diseases. To elucidate the effects of HIV infection of CD4+ T cell on the immune response to chronic **hepatitis C virus** (HCV) infection, she plans to characterize the humoral and cellular immune responses to HCV in the same subjects before and after HIV infection. Her hypothesis is that HIV infection alters CD4+ T cell by destruction or dysregulation, an effect that in turn modifies B cell and CD8+ T cell activity. Through the sponsor's research, cells, plasma, and serum have been collected before and after HIV infection from individuals with chronic HCV. Humoral responses to each HCV protein at multiple time points before and after HIV infection will be assessed using an

ELISA assay optimized for the measurement of end-point titers of IgM, IgG, and the four IgG subtypes specific for HCV CD8+ T cell responses will be measured at multiple time points before and after HIV infection using an Elispot assay for the detection of gamma interferon. Finally, the cytokine secretion profiles of CD4+ T cell will be assessed to determine if alterated cytokine production is correlated with any observed changes in B cell or T cell function. We anticipate that this study will provide insight into the impact of HIV infection on CD4+ T cell effector function, will increase understanding of HCV immune responses and control of HCV viremia, and will enhance future research aimed at elucidating the mechanisms of interaction between HIV and HCV that lead to differences in the pathogenesis and control of HCV seen with HIV co-infection. Since no direct patient contact is anticipated, Dr. Cox plans to conduct these studies through a K08 award. Dr. Cox will attend immunology, virology, and infectious disease seminars. This, along with excellent mentorship and the supportive and rich environment at JHU, will provide Dr. Cox with the skills she needs to develop into an independent researcher studying HIV/HCV coinfection immunology.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: INDUCIBLE TRANSGENIC MOUSE MODEL FOR HEPATITIS C**

  Principal Investigator & Institution: Chan, Tehsheng; Microbiology and Immunology; University of Texas Medical Br Galveston 301 University Blvd Galveston, Tx 77555

  Timing: Fiscal Year 2003; Project Start 01-JUN-2003; Project End 31-MAY-2005

  Summary: (provided by applicant): The long-range goal of this research is to develop animal models for use in elucidating the mechanism of hepatitis C, as well as in preclinical studies of candidate therapeutics. The transgenic mice that constitutively express **hepatitis C virus** (HCV) proteins in the liver have been valuable in some studies in the past. However, they have been less useful as a model for hepatitis due to their inherent tolerance to the viral antigens expressed in the liver. We have taken advantage of the cre/IoxP technology, and developed several transgenic mouse lines with inducible expression of the HCV core, E1, and E2 proteins in the liver. In this grant application, we propose studies aimed at establishing a suitable murine hepatitis C model through much improved induction technologies. We will evaluate a novel hydrodynamics-based transfection protocol. The efficiency of HCV gene induction and potential adverse effects will be examined. In addition, a cell-permeable cre fusion protein will be assessed for its function as the catalyst for HCV transgene recombination in the liver. We will then test the hypothesis that transgenic mice conditionally expressing the HCV proteins will mount immune response to the viral antigens and develop hepatitis. In the event that HCV gene expression alone is not sufficient to result in T cell homing and hepatocellular injuries, we will co-transfect the liver with a plasmid DNA encoding the co-stimulatory signal molecule CD80 or CD86 to increase the level of antigen presentation. The antibody and T cell responses against HCV antigens will then be assessed. The results obtained from these proposed studies will be the bases for future NIH RO1 grant applications.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: INHIBITION OF HEPATITIS C BY RNA LASSOS**

  Principal Investigator & Institution: Kaspar, Roger L.; Somagenics, Inc. Santa Cruz, Ca 95060

  Timing: Fiscal Year 2003; Project Start 01-AUG-2003; Project End 31-JUL-2005

Summary: (provided by investigator): The goal of this application is to develop specific RNA-based Lasso inhibitors against the hepatitis C RNA virus(HCV) and demonstrate efficacy in cell culture and animal models. RNA Lassos are proprietary antisense ribozymes that do not cleave an RNA target but rather form a topological linkage with it and block gene expression. Initial functional testing will be performed in cells expressing a bicistronic RNA containing two distinct fluorescent proteins that can be readily monitored by flow cytometry [gene expression of one cistron is dependent on the HCV internal ribosome entry site (IRES) and the other is Cap dependent]. The effect of the Lassos will be determined by the relative ratio of the activity of the two fluorescent proteins. The most effective inhibitors will be further analyzed for their ability to efficiently block expression of a reporter (HCV-luciferase construct) in mice using a hydrodynamic delivery system and whole-animal imaging system. Anti-HCV RNA Lassos will be co-injected with an HCV IRES reporter vector into mouse-tail veins under conditions of high pressure and the amount of inhibition in the liver determined. The HCV Lasso RNA inhibitors will be initially designed as semi-random molecules (library approach) that will be selected under conditions that favor specific and strong binding. Those Lassos surviving stringent conditions will be cloned and sequenced and further tested as fixed sequence molecules in a gel mobility shift assay and an in vitro translation system before evaluation in a tissue culture model and mice.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: INTERFERON RESISTANCE IN AFRICAN-AMERICANS WITH HCV**

  Principal Investigator & Institution: Layden, Thomas J.; Professor and Chief; Medicine; University of Illinois at Chicago 1737 West Polk Street Chicago, Il 60612

  Timing: Fiscal Year 2002; Project Start 01-SEP-2000; Project End 31-AUG-2004

  Summary: Hepatitis C virus infects 1.5 percent of the United States population but in African-Americans the rate approaches 5 percent. IFN has been the mainstay of therapy but the recent addition of Ribavirin has significantly improved therapeutic results with 40 percent of patients having sustained virologic clearance. However, in genotype 1 viral infection only 25 percent of patients develop sustained viral clearance. Recently, several virologic factors including genomic sequences in the NS5A and/or E2 region, have been identified as factors that promote greater resistance of genotype 1 virus to IFN. Host factors also influence response and recently, it has been demonstrated that African-Americans respond less well to IFN or IFN in combination with Ribavirin compared to Caucasians. Part of this failure may be due to the fact that greater than 90 percent of African- Americans with HCV are infected with genotype 1a or 1b virus compared to 70 percent of Caucasians. However, results suggest that response is also less in African-Americans compared to Caucasians infected with genotype 1 virus. The reason(s) for these differences in treatment response is not clear but could relate to differences in viral kinetics, IFN effectiveness, genomic sequences in the NS5A or E2 region, IFN pharmacokinetics, less immunologic response to viral infected hepatocytes or a combination of these factors. Recently, our group has detailed the kinetics of HCV. Results have shown that viral levels decrease with IFN in a biphasic manner, with the first phase accounting for a 0.5 to 2.0 log drop in RNA levels over 48 hours. This phase is explained by the effectiveness of IFN in inhibiting viral production. After this rapid drop, a second and slower phase of viral clearance ensues. This phase of RNA decline is highly variable between patients and is not dose dependent. It is theorized that this phase is dependent on immune-dependent elimination of HCV-infected liver cells. Patients having a fast reduction in viral levels clear virus early in therapy while patients who have slow or flat viral declines or viral rebound do not clear virus. We have re-

examined the response of African- Americans and Caucasians infected with genotype 1 virus who have participated in our viral kinetic studies. Initial viral load, viral half-life and viral production were similar between races. However, no African-American patient (n=12) cleared virus in the first month of IFN while 9 of 29 Caucasians cleared virus. Viral log drop at one month was 2.0 logs less in African-Americans. Initial kinetic analysis suggests that this difference is in part secondary to a lesser degree of IFN effectiveness in inhibiting viral production in African-American. However, the second phaseof viral decline was gramatically less in African-Americans reflecting either lower immunologic response to HCV infected lever cells or selection of an IFN resistant viral strain. Thus, the Specific Aims are to further define early viral kinetic differences in African-Americans versus Caucasians with IFN monotherapy and combination therapy in order to gain theoretical insight into why African-Americans respond less well to therapy; to determine whether this lack of response can be explained by differences in IFN pharmacokinetics, intrinsic viral genomic factors that have been suggested to cause IFN resistance, and/or difference in immune recognition of HCV-infected liver cells.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: JOHNS HOPKINS ADULT AIDS CLINICAL TRIALS UNIT**

  Principal Investigator & Institution: Flexner, Charles W.; Associate Professor; Medicine; Johns Hopkins University 3400 N Charles St Baltimore, Md 21218

  Timing: Fiscal Year 2002; Project Start 01-JAN-2000; Project End 31-DEC-2004

  Summary: (adapted from applicant's abstract): Johns Hopkins University has had an ACTU since its inception in 1986. The Unit is administratively within the Division of Infectious Diseases as a component of the Johns Hopkins HIV Care Program, but it is configured to make maximum use of relevant institutional resources with investigators from multiple departments and divisions including Pharmacology, Neurology, Ophthalmology, Gynecology, Pathology and Internal Medicine. The Hopkins ACTU has provided leadership to the ACTG scientific agenda and has provided HIV clinical trials to Baltimore, a city that ranks ninth among metropolitan areas in AIDS rates. The performance record for the last grant cycle shows average enrollment, data performance and a rank of No. 3 in scientific contributions. Assets of this ACTU include leadership and scientific expertise in virology (B. Jackson), immunology (H. Lederman, T. Quinn, R. Bollinger), quality of life assessment (A. Wu), neurology (J. McArthur), pharmacology (C. Flexner), CMV retinitis (D. Jabs), and mycobacteriology (R. Chaisson). This unit has a subunit in the prison system, has developed an ACTG study of tuberculosis in Haiti and has high enrollment of injection drug users and African-Americans. This application proposes to continue a scientific portfolio that has depth and diversity to support the ACTG scientific agenda and a clinical trials program that includes good data performance and the enrollment of high priority participants. All current investigators will continue in their present roles as will the three advanced technology laboratories. Three new investigators, Dr. R. Siliciano (latent reservoirs of HIV), Dr. Richard Moore (HIV outcomes, cost and cost effectiveness), and Dr. David Thomas (hepatitis C co-infection) will be added. Preference will be given to protocols that reflect emphasis areas of the Hopkins ACTU, especially pharmacology, neurology, immunology, mycobacteriology, hepatitis C, long-term outcomes (quality of life and cost analyses) and simplified ART regimens (to better serve the patients). There will be emphasis on enhanced enrollment with a new peer recruiter and a new subunit to increase the catchment area.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: LIVER STEM CELLS AND HUMANIZED MICE: A NEW MODEL FOR HCV**

  Principal Investigator & Institution: Lagasse, Eric; Stemcells, Inc. 3155 Porter Dr Palo Alto, Ca 94303

  Timing: Fiscal Year 2002; Project Start 15-FEB-2001; Project End 31-JAN-2003

  Summary: This application proposes to use NOD/SCID mice transplanted (intrasplenically or under kidney capsule) with human hepatocytes for HCV infection. The project will first identify hepatocyte subpopulations that are most susceptible to HCV infection, and examine the possible effects of hepatocyte growth factor (HGF) on hepatocyte growth in the transplanted mice. The same approach will also be applied to fumarylacetoacetate hydrolase (FAH) mice to enrich transplanted human hepatocytes. For all of the optimization procedures, hepatitis delta virus (HDV) will be used as a surrogate virus for HCV. Eventually, these humanized mice will be tested for HCV infections. PROPOSED COMMERCIAL APPLICATION: NOT AVAILABLE

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: LIVER-TARGETED PRODRUGS FOR THE TREATMENT OF HEPATITIS C**

  Principal Investigator & Institution: Linemeyer, David L.; Metabasis Therapeutics, Inc. 9390 Towne Centre Dr, Ste 200 San Diego, Ca 921213026

  Timing: Fiscal Year 2004; Project Start 01-AUG-2001; Project End 31-AUG-2005

  Summary: (provided by investigator): The long-term objective of this application is to identify a potent, efficacious and safe drug for the treatment of **hepatitis C virus** (HCV) through the use of our proprietary HepDirect prodrug technology. It is estimated that >170 million people are infected with **Hepatitis C virus** worldwide. Despite recent improvements in HCV drug formulations, a large segment of the patient population is still under treated. In the first phase of our SBIR grant support we demonstrated the potential of HepDirect prodrugs in selectively delivering high levels of phosphorylated nucleoside analogues to the liver. The work led to the identification of a development candidate (HepDirect-adefovir), which recently completed its initial Phase I clinical study and is expected to begin Phase 1/2 in early 2003. We now propose to continue the exploration of the HepDirect technology and its applications to a large and structurally-diverse set of nucleosides, with the goal of identifying a potent and selective inhibitor of HCV replication. Most nucleosides designed to be specific inhibitors of viral replication as the nucleoside triphosphate (NTP) fail as a result of poor recognition by the nucleoside kinases responsible for converting the nucleoside to the NTP. The HepDirect technology overcomes this limitation and allows us to pursue nucleoside analogues that are easily overlooked or discarded by companies pursuing standard drug discovery approaches. The specific aims of this application include the synthesis of a large number of HepDirect prodrugs of diverse nucleoside analogues, the production of the corresponding NTP library via the biological conversion of the prodrugs in hepatocytes, and the screening of this library for the inhibition of HCV replication. To support the antiviral activity determinations, a key aim is the development of a cellular assay compatible with the prodrug technology as well as a novel human tissue based HCV replication model. Following the identification of a lead inhibitor, the HepDirect prodrug moiety is optimized for intracellular activation efficiency, oral bioavailability, pharmacokinetics, as well as liver targeting. The final aim is to complete the requisite studies to launch the compound identified into full development for the treatment of

HCV including second species pharmacokinetics, pilot animal toxicology, pilot in vitro and in vivo genetic toxicology and general safety pharmacology.

Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: LIVING DONOR LIVER TRANSPLANTATION COHORT STUDY**

  Principal Investigator & Institution: Berg, Carl L.; Associate Professor; Internal Medicine; University of Virginia Charlottesville Box 400195 Charlottesville, Va 22904

  Timing: Fiscal Year 2002; Project Start 17-SEP-2002; Project End 31-AUG-2009

  Summary: (provided by applicant):As the disparity between number of potential liver transplant recipients and available cadaveric organs has widened, novel approaches have been developed to permit the successful transplantation of the largest possible number of patients with end-stage liver disease. The most promising of these strategies has involved the application of adult to adult living donor liver transplantation (LDLT). More than fifteen U.S. transplant centers have now utilized LDLT as a standard method for liver replacement. Despite the increasingly widespread application of this approach, considerable heterogeneity exists between centers regarding donor and recipient evaluation as well as the surgical techniques employed. Moreover, information is lacking regarding outcomes of this procedure for both donor and recipient, no data available to identify donors or recipients who may benefit most (or least) from this procedure, and no data to determine whether using LDLT is a cost-effective strategy. In this setting, we propose to participate as a transplant center (TC) in the LDLT Clinical Research Consortium. In this role, we propose to participate in the development of a prospective comprehensive data base and information core that will permit the dissection of the factors which lead to favorable, or unfavorable, outcomes in LDLT as compared to standard cadaveric transplantation. The existing UVA STRANDS database will permit retrospective collection of data from LDLT and cadaveric transplants performed over the last 5 years. In addition, the TC proposes to build on its institutional strengths to lead two clinical research protocols. The first protocol will develop a Cost Utility Decision Analysis using the Adult to Adult Living Donor Liver Transplantation Cohort. This research will yield a valid decision analysis model that can be used in a general patient population to better define subpopulations that would benefit from LDLT as opposed to cadaveric liver transplant. Costs and utilities to the health care system and the patients involved will be clarified for use in patient counseling, medical decision-making, and policy formulation. The second clinical research proposal will examine the outcomes of LDLT in patients infected with hepatitis C and compare these outcomes to cadaveric controls. Mechanisms that contribute to rapid allograft infection and injury will be examined including hepatocyte infection, rates of viral replication and kinetics of serum viral clearance.

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- **Project Title: MALIGNANT COMPLICATIONS OF CHRONIC HCV**

  Principal Investigator & Institution: Loffredo, Christopher A.; Assistant Professor; Oncology; Georgetown University Washington, Dc 20057

  Timing: Fiscal Year 2002; Project Start 29-SEP-1999; Project End 31-JUL-2004

  Summary: Chronic infection with **hepatitis C virus** (HCV) is a major public health problem, particularly in Egypt, where the prevalence of HCV infection is high. Among the long-term complications of HCV are hepatocellular carcinoma (HCC) and non-Hodgkin's lymphoma (NHL), but, particularly for NHL, few prospective studies have been done; hence, the incidence of malignant complications of chronic HCV is largely

unknown. The contribution of other cancer risk factors also needs to be taken into account in assessing the HCV-associated risk of HCC and of NHL. Such factors include environmental exposures to carcinogens and inherited genetic susceptibilities, and new research is needed to investigate whether these risk factors can interact with HCV to modify the risks of malignancies in persons with chronic infections. In addition, the role of tumor suppressor genes in the biology of HCC and NHL cells needs to be addressed more fully. To fill these gaps in knowledge, this proposal builds upon an ongoing collaborative infrastructure of American and Egyptian scientists and research institutions to investigate the epidemiology of HCV- associated malignancies in Egypt. We propose to conduct: (1) a case-control study of the interrelationships among viral, genetic, and environmental risk factors for these two cancers; (2) a prospective study to estimate the incidence of HCC and NHL in persons with chronic HCV; and (3) a study of the mutational spectrum of the p53 gene in the tumor tissues of patients with HCC and NHL. Given the high prevalence of both HCV and HCV- related cancers in Egypt, the high potential for environmental exposures to carcinogenic chemicals there, and our demonstrated ability to collect biological samples and to obtain high-quality data from study subjects in Egypt, this proposal represents a unique opportunity to address important questions concerning the role of hepatitis C in these types of cancers.

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- **Project Title: MIAMI ADULT AIDS CLINICAL TRIALS GROUP, AACTG**

  Principal Investigator & Institution: Fischl, Margaret A.; Associate Professor; Medicine; University of Miami-Medical Box 248293 Coral Gables, Fl 33124

  Timing: Fiscal Year 2002; Project Start 01-APR-1992; Project End 31-DEC-2004

  Summary: (adapted from application's abstract): The Miami ACTU has been a member of the AACTG since its inception and has contributed to a number of AACTG studies that led to the approval of seven antiretroviral drugs and numerous HIV treatment strategies including lower and alternative dosing schedules for all three classes of antiretroviral agents, early treatment intervention, combination therapies with dual NRTIs and triple-drug therapy. The Miami ACTU has also actively participated in the Virology Laboratory Subcommittee working groups with an active role in the standardization of a PBMC culture assay for determining drug susceptibility, the assessment of interlaboratory concordance of DNA sequencing analysis of HIV RT, and the development of a consensus sequencing protocol to detect drug resistant mutations. This unit has also been involved with the Surrogate Markers Subcommittee with an active role in the assessment of plasma cytokines and soluble markers, cytotoxic T-lymphocyte activity, lymphocyte proliferation and advanced flow cytometry, and defining and validating immunologic markers as surrogate markers independent of CD4 and HIV RNA. Finally, this unit has contributed to the Pharmacology Committee with the evaluation of targeted- concentration control studies and the correlation of drug exposure with treatment response and failure parameters. The Miami ACTU will actively participate in HIV Disease RAC efforts and provide expertise to address study treatment strategies for initial therapy, treatment options for virologic failure and utilization of phenotypic and genotypic assessments to direct subsequent therapy and treatment intensification. The Miami ACTU will also bring expertise in the areas of hepatitis B and C pathogenesis and treatment, metabolic complications of HIV-1 protease inhibitor pathogenesis and treatment, HIV dementia pathogenesis and treatment and peripheral neuropathy pain assessment, Kaposi sarcoma (KS) pathogenesis, intensive immunologic monitoring and definition, and validation of immunologic determinants of treatment response. The Miami ACTU plans to enroll 100

subjects per year across AACTG studies and 70 patients into AACTG substudies, including but limited to Compartmental, Virology, Viral Dynamics, Pharmaceuticals, Metabolic, Neurologic, Women's Health and Adherence and Outcomes substudies. With a support system in place for the long-term follow-up of patients, the Miami ACTU anticipates to enroll approximately 80 patients into the ALLRT study (ACTG 5001) over a 2-year period.

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- **Project Title: MOLECULAR STUDIES OF THE HEPATITIS C VIRUS NS2 PROTEIN**

  Principal Investigator & Institution: Yamaga, Ardath K.; Pediatrics; University of Southern California 2250 Alcazar Street, Csc-219 Los Angeles, Ca 90033

  Timing: Fiscal Year 2002; Project Start 01-SEP-2001; Project End 31-JUL-2008

  Summary: (provided by applicant) This application for the Mentored Clinical Scientist Development Award (K08) seeks support for Ardath Yamaga, M.D., who recently completed her clinical fellowship in Pediatric Gastroenterology and Nutrition and is joining the faculty at the University of Southern California Keck School of Medicine. **Hepatitis C Virus** (HCV) is estimated to affect 4 million people in the United States, approximately 2% of the population, including children. Up to 80% of those infected with HCV become chronic carriers and have an increased risk of cirrhosis, hepatocellular carcinoma and liver-related deaths. Under the mentorship of Jing-Hsiung James Ou, Ph.D., Dr. Yamaga, will continue to pursue her investigations into the molecular biology and the pathogenesis of HCV. The proposed research is focused on the HCV NS2 protein. This protein, as well as a portion of its adjacent NS3 sequence, contains a metalloprotease activity that cleaves the NS2-NS3 junction. Preliminary studies of Dr. Yamaga indicate that NS2 has multiple signal sequences and multiple transmembrane domains. This poses an interesting question regarding how NS2 mediates the cleavage of the NS2-NS3 junction. The first aim of the proposed research is to continue to investigate the molecular mechanism that regulates the membrane translocation of NS2 for the purpose of understanding its membrane topology. This membrane topology will then be used as a guide in Specific Aim 2 to study the molecular mechanism that mediates the cleavage of the NS2-NS3 junction. The hypothesis that the catalytic domain resides in the N-terminus of NS3 and that this protease domain needs to interact with the cytosolic domains of NS2 for activation will be investigated. NS2 is not required for the replication of HCV RNA. On the contrary, it interacts with the HCV envelope proteins. This raises the possibility that NS2 may be involved in viral morphogenesis and may even be a component of the virion. Thus, the third aim of the proposed research is to investigate how NS2 interacts with HCV envelope proteins and whether and how NS2 interacts with cellular proteins. The goal of this part of the research plan is to understand the biological functions of the NS2 protein. Under Dr. Ou's mentorship and with support of this award, Dr. Yamaga will acquire new knowledge and skills in the sciences of molecular biology and viral pathogenesis and develop her independent research career.

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- **Project Title: NATURAL HISTORY OF HCV INFECTION IN DRUG USERS**

  Principal Investigator & Institution: Klein, Robert S.; Professor; Montefiore Medical Center (Bronx, Ny) Bronx, Ny 104672490

  Timing: Fiscal Year 2002; Project Start 30-SEP-1999; Project End 31-AUG-2004

Summary: Hepatitis C virus (HCV) infection is a major cause of morbidity and mortality. Injection drug users have the highest prevalence of HCV infection among all populations in the U.S. at risk. We will study prospectively the natural history of HCV infection among all populations in the U.S. at risk. We will study prospectively the natural history of HCV infection in a cohort of drug users with or at risk for HIV infection. Subjects will be recruited from among participants already enrolled in a large longitudinal study of the natural history of HIV infection in drug users. We will, therefore, be able to take advantage of the large and complex sets of data being collected in that study, and we will be able to link new data that will be collecting on the natural history of HCV infection with those data. Participants will have detailed standardized interviews on demographics, medical history, sexual and drug use behaviors, HIV and immunological testing, and testing for HCV infection, including quantitative HCV RNA levels, including quantitative HCV RNA levels, HCV genotyping, anti-HCV antibodies and, in a subset of participants, HCV sequencing. Persons found to have HCV infection will be referred to the study hepatologist to be evaluated for liver disease and they will be offered standard medical therapy for their HCV infection. Our aims are to determine 1) the effects of HIV infection and its associated immunodeficiency, HCV genotype, and drug use behaviors on HCV viral load and progression of liver disease, 2) the effects of HIV infection and immunodeficiency on response to therapy for HCV infection, 3) the effects of highly active anti-retroviral therapy and control of HIV viral load on the natural history of HCV infection, and 4) whether genetic diversity of HCV is facilitated by immunodeficiency.

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- **Project Title: NON-PARENTERAL TRANSMISSION OF HEPATITIS C**

  Principal Investigator & Institution: Wang, Chia C.; Medicine; University of Washington Grant & Contract Services Seattle, Wa 98105

  Timing: Fiscal Year 2003; Project Start 01-MAY-2003; Project End 31-JAN-2008

  Summary: (provided by applicant): This proposal will provide the applicant, Chia Wang, with training in the epidemiologic study of viral transmission. Dr. Wang is a board certified ID physician with a MS in Epidemiology. During her fellowship at the University of Washington, she studied heterosexual HIV transmission in Africa. This project formed the foundation of a long term interest in the epidemiology of transmission and acquisition of infection. This proposal describes her research interests in the area of non-parenteral transmission of **hepatitis C virus** (HCV). In Aim 1, we will study individuals with chronic infection in a longitudinal study of the prevalence and pattern of shedding of HCV RNA in saliva and genital tract fluids. Furthermore, information about oral and genital tract inflammatory conditions will be collected to investigate the hypothesis that such conditions may increase shedding. In Aim 2, we explore the hypothesis that transmission may occur more efficiently during the acute phases of HCV infection. We will establish early serum viral load dynamics and mucosal shedding patterns in incident cases of HCV identified from a local cohort of HCV negative current IDUs. Finally, in Aim 3, we will examine potential risk factors in individuals who deny parenteral modes of transmission by incorporating audio computer-assisted survey instrument (ACASI) technology to reduce under-reporting bias and specific survey techniques to reduce recall bias. The under-reporting rate of stigmatized behaviors such as intravenous drug use will be determined in subjects who deny such risk factors in traditional face-to-face interviews. Reporting of other potential non-parenteral risk factors for hepatitis C, such as intranasal cocaine use, will be compared to that of a control population derived from general medicine clinic. The

mode of infection in 20-30% of hepatitis C-infected individuals remains poorly understood. The findings of the proposed research study may confirm suspected transmission routes such as sexual exposure, or may refute current figures suggesting that a substantial proportion of infections may occur non- parenterally. In addition, the proposed project will provide Dr. Wang with training in viral transmission research beyond her rather focused fellowship project, with the goal of establishing her expertise in this field and providing her with skills to pursue further independent studies in the transmission of hepatitis C and other viruses.

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- **Project Title: NOVEL ANIMAL MODELS OF HCV-RELATED HEPATOCARCINOGENESIS**

  Principal Investigator & Institution: Chung, Raymond T.; Assistant Professor of Medicine; Massachusetts General Hospital 55 Fruit St Boston, Ma 02114

  Timing: Fiscal Year 2002; Project Start 30-SEP-1999; Project End 31-AUG-2004

  Summary: (adapted from the application) **Hepatitis C virus** (HCV) infection and its complications are emerging as an extraordinarily important public health problem worldwide. Hepatocellular carcinoma (HCC) is now a firmly established and largely incurable complication of chronic HCV, and its prevalence in this country will continue to grow as a large cohort of patients infected decades ago comes to clinical attention. While most cases appear to arise in the setting of chronic inflammation, cirrhosis, and regeneration, the pathogenesis of HCV-related HCC remains unknown. It becomes apparent that a fundamental understanding of the mechanisms of HCV-related hepatocarcinogenesis is essential to effectively address this major sequel to chronic infection. Animal models of HCV-related hepatocarcinogenesis have been difficult to construct, in great part because of the obstacles to creation of a model permissive for infection. Transgenic mouse models permit the opportunity to examine the effects of selective expression of viral proteins. A recent report has suggested that transgenic mice expressing the HCV core protein alone develop HCC. We have created a transgenic mouse model that successfully expresses HCV core as well as the two envelope glycoproteins; however, these animals do not develop liver disease. The basis for these observed differences is unknown. We propose to explore the contributions of three major arms -to HCV-related HCC: (1) viral protein expression; (2) host genetic predisposition; and (3) the host immune response. To accomplish this, we will use novel transgenic mouse models to explore the direct contribution of both HCV structural to explore the mechanistic differences between our model and the core model. We will also cross our transgenic HCV structural protein mice with a recently developed mutant tumor suppressor gene mouse model that spontaneously develops HCC in a large portion of aging animals. This cross will allow us to "read out" the contribution of viral protein expression to HCC development (by increased frequency or acceleration of HCC formation), as well as to determine whether HCV-induced HCC requires a host genetic predisposition- Finally, we will create a novel, inducible transgenic model that expresses the full length HCV polyprotein to explore the contribution of activation of the host immune system to HCV-related hepatocarcinogenesis. Together, these models will help provide insights into the factors responsible for this devastating complication of chronic HCV infection.

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- **Project Title: PATHOGENESIS OF HEPATIC INJURY WITH HCV/HIV COINFECTION**

  Principal Investigator & Institution: Groopman, Jerome E.; Chief; Beth Israel Deaconess Medical Center St 1005 Boston, Ma 02215

  Timing: Fiscal Year 2002; Project Start 30-SEP-2001; Project End 31-AUG-2006

  Summary: (provided by applicant) The primary objective of this proposal is to examine how the **hepatitis C virus** (HCV) and the human immunodeficiency virus (HIV) envelope proteins may act collaboratively to trigger signaling events that contribute to hepatocyte inflammation and apoptosis. Coinfection with HIV and HCV confers a poor prognosis, with progressive hepatic dysfunction that often results in cirrhosis and death. Both intravenous drug users and hemophiliacs have a high incidence of coinfection and face this grim outcome. Why do coinfected hosts have such high rates of progressive liver disease? The pathogenesis of HCV-related hepatitis is believed to be due, in part, to immune-mediated inflammation as well as the effects of direct infection of hepatocytes. Our preliminary data suggest a novel third potential mechanism for hepatic inflammation and apoptosis. We observed in both HepG2 cells and primary hepatocytes that treatment with the HCV envelope protein E2, in conjunction with HIV gpl20, induced the inflammatory chemokine interleukin-8 (IL-8) and triggered apoptosis. These functional outcomes occurred at nanomolar concentrations of E2 and gp 120 that correspond to the Kd's for the cognate ligands binding to their respective receptors, CDS1 and CXCR4, and were associated with activation of specific signaling molecules, including the Src family Lyn kinase, RAFTK/Pyk2, Erkl/2 and p38 MAP kinases, and Fas-ligand. These data indicate that proinflammatory and apoptotic events may occur due to dual exposure to HCV and HIV envelope proteins via an "innocent bystander" mechanism. This proposal seeks to characterize the molecular mechanisms of IL-8 induction and the program of apoptosis caused by HCV E2 and HIV gpl20. A focused experimental approach is presented to delineate signaling events that originate at specific cell surface receptors, are transduced through intermediate signaling molecules, and converge on transcriptional activators of the MAP kinase family. Elucidating how these HCV and HIV envelope proteins may interact with hepatocytes could not only further our understanding of the pathogenesis of disease in coinfected hosts but also lead to targeted therapeutic strategies to improve the currently poor prognosis of such individuals.

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- **Project Title: PROTECTIVE IMMUNE RESPONSES AGAINST HEPATITIS C VIRUS**

  Principal Investigator & Institution: Nakano, Eileen T.; Hawaii Biotech, Inc. Aiea, Hi 967013900

  Timing: Fiscal Year 2002; Project Start 15-FEB-1999; Project End 31-AUG-2004

  Summary: (Adapted from Applicant's Abstract): Worldwide, 170 million people are chronically infected with **Hepatitis C virus** (HCV). Development of a safe and efficacious recombinant subunit vaccine for HCV is our long-term goal. Since the quality of the humoral response to viral envelop proteins and the breadth of the cellular response to multiple HCV proteins influence disease resolution, an HCV vaccine must be comprised of multiple HCV proteins and utilize a strategy which elicits broad based immunity. Feasibility of this approach was demonstrated in Phase I research within the production of five viral structural proteins. These proteins appear to have native-like structure, and each has specific attributes which make them attractive as subunit vaccine

candidates. In Phase II research additional HCV proteins will be produced. Mice will be immunized with individual and combinations of proteins, and the composition of the humoral response and the extent and type of cellular response elicited will be evaluated. By dissecting the immune response, a vaccine strategy can be defined which maximizes each subunit's potential. In the last year of Phase II research, the identified vaccine strategy will be tested in primates. The information generated from Phase II research represents a crucial step in developing a multi-component vaccine against HCV. PROPOSED COMMERCIAL APPLICATION: NOT AVAILABLE

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- **Project Title: RACIAL DIFFERENCE IN HCV/HOST INTERACTIONS**

  Principal Investigator & Institution: Riely, Caroline A.; Professor; Medicine; University of Tennessee Health Sci Ctr Memphis, Tn 38163

  Timing: Fiscal Year 2002; Project Start 01-AUG-2000; Project End 31-MAY-2005

  Summary: The University of Tennessee, Memphis Hepatitis C Cooperative Research Center will use studies of HCV/host interactions to determine why African American patients with HCV respond poorly to standard therapy (interferon and ribavirin). Hepatitis C is common, 1.8% of all Americans, but is even more common among African Americans, and in persons living in poverty. In Memphis, 55% of the population is African American, 34% of whom live below the poverty line. In a previous study, we documented a response rate of only 5% in this population, contrasted with 40% in whites. We propose to systematically characterize the differences between African Americans and whites by allelic variations in cellular ligands/receptors for HCV (Project 1). In Project 2, we will continue to develop an in vitro system for studying HCV, a chimeric VSV virus with the hepatitis C E1 and E2 envelope proteins expressed on its surface. We will use this model to characterize virus/cell interactions, testing antibodies to specific dominant quasispecies, contrasting our African American patients with whites. We will further characterize the putative receptor for HCV, CD81, to define its associated proteins, possible co-receptors (Project 3). These data will interface back to our patients as we search for allelic variations between African Americans and whites to explain the differences in response to therapy. Using the surrogate virus model, we will also screen libraries of small molecules to search for compounds that can block E2/CD81 binding (Project # African American population responds so poorly. Understanding this phenomenon will provide insights into why present day therapy is still only moderately successful in all populations, will allow us to predict who is more likely to respond, and will pave the way to developing better therapy for this emerging health problem.

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- **Project Title: ROLE OF LIVER CYTOKINES IN HEPATITIS C VIRAL INFECTION**

  Principal Investigator & Institution: Liu, Chen; Assistant Professor; Pathology, Immunol & Lab Med; University of Florida Gainesville, Fl 32611

  Timing: Fiscal Year 2002; Project Start 01-SEP-2002; Project End 31-AUG-2007

  Summary: (provided by applicant): **Hepatitis C virus** (HCV) infection is a major cause of chronic liver disease and liver cancer, and is the most common indication for liver transplantation in the United States. The hallmarks of the HCV infection are viral persistence and liver cell injury. The underlying molecular mechanisms remain poorly understood. Cytokines appear to play a critical role in viral clearance and liver tissue damage. The Long-Term Goal of our research program is to understand how antiviral cytokines modulate viral RNA replication and the predictive role of these cytokines in

response to interferon alpha treatment. In support of this goal, our Preliminary Studies have 1) demonstrated that IFN` and FGF1 have a direct effect on HCV viral subgenomic RNA (replicon) replication in hepatoma cells; 2) identified several IFN` responsive genes potentially responsible for its antiviral activity in the replicon cell lines; 3) established a cytokine-related cDNA microarray system and established the feasibility of carrying out microarray experiment using liver biopsy tissues. These studies have led us to formulate a Central Hypothesis of this proposal, that antiviral cytokines such as IFN` or others are critical in viral clearance by direct inhibition of viral replication within hepatocytes; and the presence of these cytokines before IFN` treatment can predict the responsiveness to the therapy. In the Specific Aims we will: 1) determine the efficacy of cytokines such as IFN` and FGF1 on inhibiting HCV viral RNA replication and to identify the key intracellular signaling molecules responsible for this effect; and 2) identify cytokines that favor viral clearance versus viral persistence through analyzing HCV-infected liver tissues before and after IFN-based treatment. To address these aims, we will utilize the existing HCV replicon cell line for in vitro mechanistic studies and carry out microarray experiments using liver biopsy tissues to determine the role of antiviral cytokines in HCV-infected patients. This proposal will delineate how IFN` and FGF1 exert antiviral activity within hepatocytes, and will identify cytokines that predict viral clearance in HCV viral infection. This study will enhance our understanding of the host and **hepatitis C virus** interactions underlying the pathogenesis of viral chronic infection. The candidate's long-term career goal is to be an independent physician scientist conducting translational research. The immediate career goal is to develop the scientific reasoning and skills necessary for a successful research career by carrying out the current research proposal. Our institution provides an outstanding supportive environment for career development. This funding mechanism will give the candidate the opportunity to establish an independent research career.

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- **Project Title: SELECTIVE INHIBITION OF HCV TRANSLATION BY TETRAPEPTIDE**

  Principal Investigator & Institution: Birk, Alexander V.; Biochemistry; Weill Medical College of Cornell Univ New York, Ny 10021

  Timing: Fiscal Year 2004; Project Start 01-AUG-2004; Project End 31-JUL-2009

  Summary: (provided by applicant): **Hepatitis C virus** (HCV) is a major cause of chronic liver disease, liver cirrhosis and hepatocellular carcinoma. Preliminary studies with a water-soluble, cell-permeable and non-cytotoxic synthetic peptide called DAPL (Dmt-D-Arg-Phe-Lys-NH2, where Dmt is 2', 6'- dimethyltyrosine) demonstrate that this peptide can selectively interact with the HCV RNA translation initiation site (HCV IRES) and inhibit HCV translation selectively in vitro. The goal of this proposal is to explore the biochemistry, pharmacology and mechanism of action of DAPL in inhibiting HCV translation, the key element of HCV infection. Three specific aims were established: (1) Studies on regulation of HCV-IRES-mediated translation by DAPL in vitro. Thus, we plan to demonstrate an effect of DAPL on HCV translation in vitro and determine the site(s) of DAPL-IRES interaction, by determining the sites of the IRES protected by DAPL from enzymatic, chemical, and physical probing. We will also determine the effect of DAPL on ribosomal assembly on HCV IRES, by determining the effect of DAPL on HCV RNA binding to ribosomal subunits and the ribosomal protection of HCV IRES from RNase digestion. (2) To examine the ability of DAPL to regulate HCV translation and replication in cells. Thus, the effect of DAPL on HCV IRES-directed translation and HCV RNA synthesis in Huh 7 and Huh-7.5 cells transfected with DNA vectors carrying

reporters (luciferase) and HCV replicon, respectively will be determined with Northern and Western assays. (3) To investigate structural requirements of DAPL for selective inhibition of HCV translation. Thus, we plan to investigate the role of dimethyl-tyrosine, arginine, and different lengths terminal lysines in the regulation of HCV translation in vitro and their interaction with HCV IRES. If DAPL or related analogues can be further developed to target and inhibit HCV RNA translation, the clinical application of this kind of therapeutics might be significant.

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- **Project Title: SEQUENCE SELECTION AND PERSISTENCE OF HEPATITIS C**

  Principal Investigator & Institution: Ray, Stuart C.; Associate Professor; Medicine; Johns Hopkins University 3400 N Charles St Baltimore, Md 21218

  Timing: Fiscal Year 2002; Project Start 30-SEP-1999; Project End 31-AUG-2004

  Summary: (adapted from the application) The mechanisms of persistence of **hepatitis C virus** (HCV) infection are poorly understood, but the highly mutable viral genome offers a window on the natural history of this process. Whereas inadequate in vitro and animal models have hampered efforts to observe the virus more directly, sequence analysis has identified strains with higher pathogenic potential and resistance to pharmacologic treatment. It is not surprising that HCV sequences reveal clues to pathogenesis, because HCV exists in each infected host as a quasispecies. (a swarm of distinct but related variants), which is subject to Darwinian selection by the host's immune system. We have developed a method to identify distinct variants in each infected individual, allowing us to acquire an accurate nucleotide sequence sample of the quasispecies at greatly reduced cost. We also have access to specimens from ALIVE, a large cohort of injecting drug users, with clearly defined clinical and virologic outcomes. Our preliminary studies of acute infection suggest that self-limited viremia is associated with a less complex swarm of HCV variants, greater host selective pressure on more conserved regions (based on the ratio of within-quasispecies non-synonymous to synonymous diversity), and higher positive charge at the highly variable N-terminus of the envelope protein E2. Our central hypothesis is that an immune response directed against more conserved epitopes is associated with clearance of HCV viremia following acute infection. By testing this hypotheses in a well-characterized cohort with years of clinical and virologic data, we anticipate success in achieving greater understanding of antigenic variation as it relates to quasispecies diversity, and of the mechanisms of HCV persistence. Greater understanding of these aspects of HCV pathogenesis would have a significant impact on vaccine development and rational drug design. By combining our epidemiologic and molecular resources with novel tools, we aim to confirm and extend our preliminary observations by (1) studying a validation cohort, (2) collecting longitudinal sequence data, and (3) expanding the scope of the analysis to include more conserved regions of the HCV genome. This application is efficient and has a high likelihood of success because it makes use of a well-characterized cohort, for which years of clinical and virologic data have already been assembled.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: STRUCTURAL ANALYSIS OF THE HEPATITIS C CORE PROTEIN**

  Principal Investigator & Institution: Allaire, Marc; Brookhaven Science Assoc-Brookhaven Lab Brookhaven National Lab Upton, Ny 11973

  Timing: Fiscal Year 2003; Project Start 30-SEP-2003; Project End 31-JAN-2006

Summary: (provided by applicant): **Hepatitis C virus** (HCV) infection is recognized as a worldwide health problem affecting over 170 million individuals. In the United States, over 4 million peoples have been infected and 12,000 deaths yearly are due to hepatitis C. HCV is the most common reason for liver transplantation and accounts for one-third of hepatocellular carcinoma. Prevention of the HCV infection is impeded by the lack of protective vaccines and current therapies against HCV are unsatisfactory. There is clearly an urgent need for the development of new drugs. The molecular mechanisms of viral replication and viral assembly of HCV are poorly understood. It has been shown recently that nucleocapsid-like particles of HCV can be assembled from the HCV core protein that are identical to the HCV nucleocapsid from sera of infected patients. The aim of this proposal is to characterize the HCV core and capsid using macromolecular crystallography and to characterize the packaging signal on the viral RNA. The HCV core protein is the viral subunit of the HCV capsid. It appeared in the last few years that this protein is also very important for the pathogenesis of the disease by inducing cancer, cirrhosis and inflammation of the liver tissue. The resolution of the three-dimensional structure of this protein and the capsid will not only help us to characterize the protein-protein interactions between the proteins subunits, the interaction between the subunits and the nucleic acid but also to resolve the surface of the capsid that interacts with several host factors responsible for different aspects of the pathogenesis of the disease. Altogether, the determination of the structure of the capsid will facilitate the development of research programs that aim to inhibit the assembly of the virus, a novel and very promising target for drug development.

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- **Project Title: STRUCTURE AND MECHANISM OF INTERNAL RIBOSOME ENTRY SITES**

  Principal Investigator & Institution: Doudna, Jennifer A.; Professor; Molecular and Cell Biology; University of California Berkeley Berkeley, Ca 947205940

  Timing: Fiscal Year 2002; Project Start 01-SEP-2002; Project End 31-AUG-2006

  Summary: (provided by applicant): The initiation of protein synthesis is a key step in the gene expression pathway, requiring recruitment and correct positioning of ribosomes on mRNA templates in a process that is highly regulated in all cells. A subset of eukaryotic genes and viruses circumvent the usual cellular controls on initiation by utilizing structured RNAs called internal ribosome entry sites (IRESs) to direct ribosomes to the translational start codon. This project aims to elucidate the mechanism of internal translation initiation by focusing on the IRES elements of **Hepatitis C virus** (HCV), a major human pathogen, and the cellular c-myc gene, involved in cell growth and transformation. X-ray crystallography will be used to solve molecular structures of functional domains as well as full-length constructs of the HCV IRES RNA, providing a structural basis for exploring IRES interactions with the translational apparatus. Using both cryo-electron microscopy and X-ray crystallography, complexes of the IRES bound to 40S subunits with and without initiation factors will be analyzed. The cryo-EM work will be carried out in an ongoing collaboration with Prof. Joachim Frank, and will guide preparation and crystallization of functional complexes. Structures determined in this part of the study will provide the basis for addressing how the IRES positions the mRNA correctly in the ribosomal decoding center, and how initiation factors influence this assembly process. They will also provide the first images of the human ribosome, enabling comparison with crystallographic and cryo-EM structures of the bacterial, archaeal and yeast ribosomes and subunits. To compare the structural and functional properties of a viral versus a cellular IRES, we will investigate the folding and

mechanism of action of the cellular c-myc IRES. Results from this work will yield a detailed mechanistic understanding of one of the fundamental processes in gene expression, and may lead to methods for inhibition of IRES activity.

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- **Project Title: T LYMPHOCYTE APOPTOSIS IN HEPATITIS C PERSISTENCE**

  Principal Investigator & Institution: Koziel, Margaret J.; Assistant Professor; Beth Israel Deaconess Medical Center St 1005 Boston, Ma 02215

  Timing: Fiscal Year 2002; Project Start 01-AUG-2002; Project End 31-JUL-2007

  Summary: (provided by applicant): **Hepatitis C virus** (HCV) infection has been increasingly recognized as a major cause of chronic hepatitis, liver cirrhosis and hepatocellular carcinoma (HCC). The proportion of individuals infected more than twenty years, who face the highest rate of complications, is expected to increase over the next ten to twenty years. Approximately 85 percent of infected individuals fail to clear the virus. A central unresolved issue in HCV infection is how the virus establishes persistent infection in most infected individuals. A number of recent studies have suggested that failure of HCV clearance is associated with weakness in 1-cell responses against the virus. Although HCV-specific T cells are readily demonstrable in most chronically infected individuals, their frequency in the liver and peripheral blood is unusually low, when compared with other viral infections. It is not clear whether this is due to failure of generating virus-specific T-cell response or due to increased apoptosis of activated effector 1 cells. Accumulating evidence has shown that the liver may play an important role in T cell homeostasis by trapping and eliminating activated T cells, especially CD8+ 1 cells. The central hypothesis of this proposal is that hepatocytes infected by HCV causes premature apoptosis of HCV-specific T cells in the liver, leading to attenuation of T-cell response. In support of this hypothesis, our preliminary studies have shown that apoptosis of activated CD4+ and CD8+ T cells was accelerated after exposure to hepatocytes expressing HCV core, El and E2 transgenes either in vitro or in vivo. This was accompanied by up-regulation of the expression of Fas ligand (FasL or Apo- I ligand), one of the death-inducing molecules, in transgenic hepatocytes, and could be blocked by antibodies against Fas in vitro and in vivo. The experiments proposed here are specifically designed to extend our observations, and to validate our hypothesis in vivo. Specifically, we propose to: 1) Determine the in vivo significance of increased T lymphocyte apoptosis in HCV transgenic mice; 2) Determine whether Fas: FasL interactions are critical to apoptosis of activated T cells in this system; and 3) Characterize the HCV proteins regulating apoptosis of activated T lymphocytes using novel adeno-associated virus vectors to express HCV proteins in murine hepatocytes. These data would confirm one mechanism of HCV persistence may be attenuation of the immune response in the principal site of viral replication, and might suggest new therapeutic strategies to augment the effectiveness of the immune response.

  Website: http://crisp.cit.nih.gov/crisp/Crisp_Query.Generate_Screen

- **Project Title: THE EPIDEMIOLOGY OF HEPATITIS C INFECTION IN THAILAND**

  Principal Investigator & Institution: Nelson, Kenrad E.; Professor; Epidemiology; Johns Hopkins University 3400 N Charles St Baltimore, Md 21218

  Timing: Fiscal Year 2002; Project Start 20-SEP-1999; Project End 31-AUG-2004

  Summary: The proposed research program will involve integrated collaborative studies of the epidemiology, biology and natural history of **hepatitis C virus** (HCV) infections in Northern Thailand. Infections with HCV are a worldwide health problem and are a

major cause of chronic liver disease, liver cancer and cirrhosis. It is estimated that 4 million persons in the United States and 180 million persons worldwide are infected with HCV. After infection 80 percent of individuals will become chronic carriers and 20 percent of them will progress to chronic liver disease or cancer in the next 15-20 years. Epidemiologic studies in some populations have found high rates of HCV in injection drug users and lower but elevated rates from sexual and perinatal transmission. However, infections in many individuals are cryptogenic. The reasons for the persistence of HCV infection in such a high proportion of infected individuals is not clear. However, the virus is genetically quite diverse and viral variation with the emergence of new quasispecies usually occurs in chronically infected people. Furthermore the epidemiology and transmission of HCV is intertwined with HIV, so many persons who are infected with both viruses may be immunosuppressed. The studies we have planned will involve comprehensive investigations of the epidemiology, virology and natural history of HCV infections in various populations in Northern Thailand, most of whom are being evaluated for HIV infection. Liver cancer is one of the leading causes of cancer in Thailand and HCV prevalence in blood donors is 8-10 fold greater than in the U.S. The study populations will include injection drug users, sex workers, STD patients, military recruits, blood donors and their spouses and general community populations. Through the transfer of technology for HCV research to our collaborators, we hope to focus on understanding the biology and epidemiology of HCV and the development of more effective prevention of HCV.

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E-Journals: PubMed Central[3]

PubMed Central (PMC) is a digital archive of life sciences journal literature developed and managed by the National Center for Biotechnology Information (NCBI) at the U.S. National Library of Medicine (NLM).[4] Access to this growing archive of e-journals is free and unrestricted.[5] To search, go to **http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=Pmc**, and type "hepatitis C virus" (or synonyms) into the search box. This search gives you access to full-text articles. The following is a sample of items found for hepatitis C virus in the PubMed Central database:

- **3[prime prime or minute] Nontranslated RNA Signals Required for Replication of Hepatitis C Virus RNA.** by Yi M, Lemon SM.; 2003 Mar 15; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=149512
- **A cis-Acting Replication Element in the Sequence Encoding the NS5B RNA-Dependent RNA Polymerase Is Required for Hepatitis C Virus RNA Replication.** by You S, Stump DD, Branch AD, Rice CM.; 2004 Feb 1; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=321395
- **A comparison of the molecular clock of hepatitis C virus in the United States and Japan predicts that hepatocellular carcinoma incidence in the United States will**

[3] Adapted from the National Library of Medicine: **http://www.pubmedcentral.nih.gov/about/intro.html**.

[4] With PubMed Central, NCBI is taking the lead in preservation and maintenance of open access to electronic literature, just as NLM has done for decades with printed biomedical literature. PubMed Central aims to become a world-class library of the digital age.

[5] The value of PubMed Central, in addition to its role as an archive, lies in the availability of data from diverse sources stored in a common format in a single repository. Many journals already have online publishing operations, and there is a growing tendency to publish material online only, to the exclusion of print.

increase over the next two decades. by Tanaka Y, Hanada K, Mizokami M, Yeo AE, Shih JW, Gojobori T, Alter HJ.; 2002 Nov 26;
http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=137760

- **A Natural Intergenotypic Recombinant of Hepatitis C Virus Identified in St. Petersburg.** by Kalinina O, Norder H, Mukomolov S, Magnius LO.; 2002 Apr 15;
http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=136067
- **A Phylogenetically Conserved Stem-Loop Structure at the 5[prime prime or minute] Border of the Internal Ribosome Entry Site of Hepatitis C Virus Is Required for Cap-Independent Viral Translation.** by Honda M, Beard MR, Ping LH, Lemon SM.; 1999 Feb;
http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=103937
- **A Recombinant Hepatitis C Virus RNA-Dependent RNA Polymerase Capable of Copying the Full-Length Viral RNA.** by Oh JW, Ito T, Lai MM.; 1999 Sep;
http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=104296
- **A Retention Signal Necessary and Sufficient for Endoplasmic Reticulum Localization Maps to the Transmembrane Domain of Hepatitis C Virus Glycoprotein E2.** by Cocquerel L, Meunier JC, Pillez A, Wychowski C, Dubuisson J.; 1998 Mar;
http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=109514
- **A Serotyping Assay for Hepatitis C Virus in Southeast Asia.** by Songsivilai S, Kanistanon D, Dharakul T.; 1998 Sep;
http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=95649
- **A Small Yeast RNA Blocks Hepatitis C Virus Internal Ribosome Entry Site (HCV IRES)-Mediated Translation and Inhibits Replication of a Chimeric Poliovirus under Translational Control of the HCV IRES Element.** by Das S, Ott M, Yamane A, Tsai W, Gromeier M, Lahser F, Gupta S, Dasgupta A.; 1998 Jul;
http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=110227
- **Abnormal Priming of CD4 + T Cells by Dendritic Cells Expressing Hepatitis C Virus Core and E1 Proteins.** by Sarobe P, Lasarte JJ, Casares N, Lopez-Diaz de Cerio A, Baixeras E, Labarga P, Garcia N, Borras-Cuesta F, Prieto J.; 2002 May 15;
http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=136154
- **Accurate quantification of hepatitis C virus (HCV) RNA from all HCV genotypes by using branched-DNA technology.** by Detmer J, Lagier R, Flynn J, Zayati C, Kolberg J, Collins M, Urdea M, Sanchez-Pescador R.; 1996 Apr;
http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&rendertype=abstract&artid=228914
- **Activation of the Interferon-Inducible 2[prime prime or minute]-5[prime prime or minute]-Oligoadenylate Synthetase Gene by Hepatitis C Virus Core Protein.** by Naganuma A, Nozaki A, Tanaka T, Sugiyama K, Takagi H, Mori M, Shimotohno K, Kato N.; 2000 Sep 15;
http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=116387
- **Acute Hepatitis C Virus Structural Gene Sequences as Predictors of Persistent Viremia: Hypervariable Region 1 as a Decoy.** by Ray SC, Wang YM, Laeyendecker O, Ticehurst JR, Villano SA, Thomas DL.; 1999 Apr;
http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=104053

- **Alpha Interferon Induces Distinct Translational Control Programs To Suppress Hepatitis C Virus RNA Replication.** by Wang C, Pflugheber J, Sumpter, Jr. R, Sodora DL, Hui D, Sen GC, Gale, Jr. M.; 2003 Apr 1; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=150642
- **Alpha Interferon Inhibits Hepatitis C Virus Replication in Primary Human Hepatocytes Infected In Vitro.** by Castet V, Fournier C, Soulier A, Brillet R, Coste J, Larrey D, Dhumeaux D, Maurel P, Pawlotsky JM.; 2002 Aug 15; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=155162
- **Alterations to both the Primary and Predicted Secondary Structure of Stem-Loop IIIc of the Hepatitis C Virus 1b 5[prime prime or minute] Untranslated Region (5[prime prime or minute]UTR) Lead to Mutants Severely Defective in Translation Which Cannot Be Complemented in trans by the Wild-Type 5[prime prime or minute]UTR Sequence.** by Tang S, Collier AJ, Elliott RM.; 1999 Mar; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=104481
- **Amphipathic Helix-Dependent Localization of NS5A Mediates Hepatitis C Virus RNA Replication.** by Elazar M, Cheong KH, Liu P, Greenberg HB, Rice CM, Glenn JS.; 2003 May 15; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=154017
- **Analysis of hepatitis C virus isolates by serotyping and genotyping.** by van Doorn LJ, Kleter B, Pike I, Quint W.; 1996 Jul; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&rendertype=abstract&artid=229115
- **Antiapoptotic and Oncogenic Potentials of Hepatitis C Virus Are Linked to Interferon Resistance by Viral Repression of the PKR Protein Kinase.** by Gale M Jr, Kwieciszewski B, Dossett M, Nakao H, Katze MG.; 1999 Aug; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=112733
- **Antigenic Heterogeneity of the Hepatitis C Virus NS5A Protein.** by Dou XG, Talekar G, Chang J, Dai X, Li L, Bonafonte MT, Holloway B, Fields HA, Khudyakov YE.; 2002 Jan; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=120141
- **Antigenic structure of the complete nonstructural (NS) 2 and 5 proteins of hepatitis C virus (HCV): anti-HCV NS2 and NS5 antibody reactivities in relation to HCV serotype, presence of HCV RNA, and acute HCV infection.** by Zhang ZX, Chen M, Sonnerborg A, Sallberg M.; 1994 May; http://www.pubmedcentral.gov/picrender.fcgi?tool=pmcentrez&action=stream&blobtype=pdf&artid=368250
- **Antigenicity and Immunogenicity of Novel Chimeric Hepatitis B Surface Antigen Particles with Exposed Hepatitis C Virus Epitopes.** by Netter HJ, Macnaughton TB, Woo WP, Tindle R, Gowans EJ.; 2001 Mar 1; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=114797
- **Antisense Oligonucleotide Inhibition of Hepatitis C Virus (HCV) Gene Expression in Livers of Mice Infected with an HCV-Vaccinia Virus Recombinant.** by Zhang H, Hanecak R, Brown-Driver V, Azad R, Conklin B, Fox MC, Anderson KP.; 1999 Feb; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=89075

- **Antisense oligonucleotides targeted to the domain IIId of the hepatitis C virus IRES compete with 40S ribosomal subunit binding and prevent in vitro translation.** by Tallet-Lopez B, Aldaz-Carroll L, Chabas S, Dausse E, Staedel C, Toulme JJ.; 2003 Jan 15; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=140505
- **Antiviral Effect and Virus-Host Interactions in Response to Alpha Interferon, Gamma Interferon, Poly(I)-Poly(C), Tumor Necrosis Factor Alpha, and Ribavirin in Hepatitis C Virus Subgenomic Replicons.** by Lanford RE, Guerra B, Lee H, Averett DR, Pfeiffer B, Chavez D, Notvall L, Bigger C.; 2003 Jan 15; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=140845
- **Assessment of Hepatitis C Virus Sequence Complexity by Electrophoretic Mobilities of Both Single-and Double-Stranded DNAs.** by Wang YM, Ray SC, Laeyendecker O, Ticehurst JR, Thomas DL.; 1998 Oct; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=105098
- **Assessment, by Transcription-Mediated Amplification, of Virologic Response in Patients with Chronic Hepatitis C Virus Treated with Peginterferon [alpha]-2a.** by Sarrazin C, Hendricks DA, Sedarati F, Zeuzem S.; 2001 Aug; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=88249
- **At Least 12 Genotypes of Hepatitis C Virus Predicted by Sequence Analysis of the Putative E1 Gene of Isolates Collected Worldwide.** by Bukh J, Purcell RH, Miller RH.; 1993 Sep 1; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&rendertype=abstract&artid=47323
- **Automated Multiplex Assay System for Simultaneous Detection of Hepatitis B Virus DNA, Hepatitis C Virus RNA, and Human Immunodeficiency Virus Type 1 RNA.** by Meng Q, Wong C, Rangachari A, Tamatsukuri S, Sasaki M, Fiss E, Cheng L, Ramankutty T, Clarke D, Yawata H, Sakakura Y, Hirose T, Impraim C.; 2001 Aug; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=88264
- **Automated RIBA Hepatitis C Virus (HCV) Strip Immunoblot Assay for Reproducible HCV Diagnosis.** by Martin P, Fabrizi F, Dixit V, Quan S, Brezina M, Kaufman E, Sra ,K, DiNello R, Polito A, Gitnick G.; 1998 Feb; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=104547
- **Binding of Hepatitis C Virus E2 Glycoprotein to CD81 Does Not Correlate with Species Permissiveness to Infection.** by Meola A, Sbardellati A, Bruni Ercole B, Cerretani M, Pezzanera M, Ceccacci A, Vitelli A, Levy S, Nicosia A, Traboni C, McKeating J, Scarselli E.; 2000 Jul 1; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=112089
- **Biochemical properties of hepatitis C virus NS5B RNA-dependent RNA polymerase and identification of amino acid sequence motifs essential for enzymatic activity.** by Lohmann V, Korner F, Herian U, Bartenschlager R.; 1997 Nov; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&rendertype=abstract&artid=192304
- **Biosynthesis and biochemical properties of the hepatitis C virus core protein.** by Santolini E, Migliaccio G, La Monica N.; 1994 Jun; http://www.pubmedcentral.gov/picrender.fcgi?tool=pmcentrez&action=stream&blobtype=pdf&artid=236867

- **Both NS3 and NS4A are required for proteolytic processing of hepatitis C virus nonstructural proteins.** by Failla C, Tomei L, De Francesco R.; 1994 Jun; http://www.pubmedcentral.gov/picrender.fcgi?tool=pmcentrez&action=stream&blobtype=pdf&artid=236880
- **Cationic phosphoramidate [alpha]-oligonucleotides efficiently target single-stranded DNA and RNA and inhibit hepatitis C virus IRES-mediated translation.** by Michel T, Martinand-Mari C, Debart F, Lebleu B, Robbins I, Vasseur JJ.; 2003 Sep 15; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=203318
- **CD81 Is Required for Hepatitis C Virus Glycoprotein-Mediated Viral Infection.** by Zhang J, Randall G, Higginbottom A, Monk P, Rice CM, McKeating JA.; 2004 Feb 1; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=321402
- **Cell Fusion Activity of Hepatitis C Virus Envelope Proteins.** by Takikawa S, Ishii K, Aizaki H, Suzuki T, Asakura H, Matsuura Y, Miyamura T.; 2000 Jun 1; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=110858
- **Cell Surface Expression of Major Histocompatibility Complex Class I Molecules Is Reduced in Hepatitis C Virus Subgenomic Replicon-Expressing Cells.** by Tardif KD, Siddiqui A.; 2003 Nov 1; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=229359
- **Cell Type-Specific Enhancement of Hepatitis C Virus Internal Ribosome Entry Site-Directed Translation due to 5[prime prime or minute] Nontranslated Region Substitutions Selected during Passage of Virus in Lymphoblastoid Cells.** by Lerat H, Shimizu YK, Lemon SM.; 2000 Aug 1; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=112219
- **Cell-Free Replication of the Hepatitis C Virus Subgenomic Replicon.** by Ali N, Tardif KD, Siddiqui A.; 2002 Dec 1; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=136887
- **Characterization of a Monoclonal Antibody and Its Single-Chain Antibody Fragment Recognizing the Nucleoside Triphosphatase/Helicase Domain of the Hepatitis C Virus Nonstructural 3 Protein.** by Zhang ZX, Lazdina U, Chen M, Peterson DL, Sallberg M.; 2000 Jan; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=95823
- **Characterization of Cell Lines Carrying Self-Replicating Hepatitis C Virus RNAs.** by Pietschmann T, Lohmann V, Rutter G, Kurpanek K, Bartenschlager R.; 2001 Feb 1; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=114031
- **Characterization of Hepatitis C Virus (HCV) and HCV E2 Interactions with CD81 and the Low-Density Lipoprotein Receptor.** by Wunschmann S, Medh JD, Klinzmann D, Schmidt WN, Stapleton JT.; 2000 Nov 1; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=102044
- **Characterization of Hepatitis C Virus Quasispecies by Matrix-Assisted Laser Desorption Ionization-Time of Flight (Mass Spectrometry) Mutation Detection.** by Ayers M, Siu K, Roberts E, Garvin AM, Tellier R.; 2002 Sep; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=130814
- **Characterization of Low- and Very-Low-Density Hepatitis C Virus RNA-Containing Particles.** by Andre P, Komurian-Pradel F, Deforges S, Perret M, Berland JL, Sodoyer M, Pol S, Brechot C, Paranhos-Baccala G, Lotteau V.; 2002 Jul 15; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=136313

- **Characterization of Soluble Hepatitis C Virus RNA-Dependent RNA Polymerase Expressed in Escherichia coli.** by Ferrari E, Wright-Minogue J, Fang JW, Baroudy BM, Lau JY, Hong Z.; 1999 Feb; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=103993
- **Characterization of the Hepatitis C Virus NS2/3 Processing Reaction by Using a Purified Precursor Protein.** by Pallaoro M, Lahm A, Biasiol G, Brunetti M, Nardella C, Orsatti L, Bonelli F, Orru S, Narjes F, Steinkuhler C.; 2001 Oct 15; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=114565
- **Characterization of the Inhibition of Hepatitis C Virus RNA Replication by Nonnucleosides.** by Tomei L, Altamura S, Bartholomew L, Bisbocci M, Bailey C, Bosserman M, Cellucci A, Forte E, Incitti I, Orsatti L, Koch U, De Francesco R, Olsen DB, Carroll SS, Migliaccio G.; 2004 Jan 15; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=368780
- **Characterization of Vesicular Stomatitis Virus Recombinants That Express and Incorporate High Levels of Hepatitis C Virus Glycoproteins.** by Buonocore L, Blight KJ, Rice CM, Rose JK.; 2002 Jul 15; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=136334
- **Charged Residues in the Transmembrane Domains of Hepatitis C Virus Glycoproteins Play a Major Role in the Processing, Subcellular Localization, and Assembly of These Envelope Proteins.** by Cocquerel L, Wychowski C, Minner F, Penin F, Dubuisson J.; 2000 Apr 15; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=111872
- **Chimeric hepatitis B virus core particles with parts or copies of the hepatitis C virus core protein.** by Yoshikawa A, Tanaka T, Hoshi Y, Kato N, Tachibana K, Iizuka H, Machida A, Okamoto H, Yamasaki M, Miyakawa Y, et al.; 1993 Oct; http://www.pubmedcentral.gov/picrender.fcgi?tool=pmcentrez&action=stream&blobtype=pdf&artid=238027
- **Classification of Hepatitis C Virus Type 2 Isolates by Phylogenetic Analysis of Core and NS5 Regions.** by Pistello M, Maggi F, Fornai C, Leonildi A, Morrica A, Vatteroni ML, Bendinelli M.; 1999 Jun; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=85058
- **Clearance of replicating hepatitis C virus replicon RNAs in cell culture by small interfering RNAs.** by Randall G, Grakoui A, Rice CM.; 2003 Jan 7; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=140937
- **Clinical Evaluation of the Automated COBAS AMPLICOR HCV MONITOR Test Version 2.0 for Quantifying Serum Hepatitis C Virus RNA and Comparison to the Quantiplex HCV Version 2.0 Test.** by Yu ML, Chuang WL, Dai CY, Chen SC, Lin ZY, Hsieh MY, Wang LY, Chang WY.; 2000 Aug; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=87152
- **Clinical Evaluation of Two Methods for Genotyping Hepatitis C Virus Based on Analysis of the 5[prime prime or minute] Noncoding Region.** by Nolte FS, Green AM, Fiebelkorn KR, Caliendo AM, Sturchio C, Grunwald A, Healy M.; 2003 Apr; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=153875
- **Clinical Significance of Hepatitis C Virus Genotypes.** by Zein NN.; 2000 Apr; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=100152
- **Comparative Analysis of Translation Efficiencies of Hepatitis C Virus 5[prime prime or minute] Untranslated Regions among Intraindividual Quasispecies Present in**

Chronic Infection: Opposite Behaviors Depending on Cell Type. by Laporte J, Malet I, Andrieu T, Thibault V, Toulme JJ, Wychowski C, Pawlotsky JM, Huraux JM, Agut H, Cahour A.; 2000 Nov 15;
http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=110962

- **Comparative Evaluation of the Total Hepatitis C Virus Core Antigen, Branched-DNA, and Amplicor Monitor Assays in Determining Viremia for Patients with Chronic Hepatitis C during Interferon Plus Ribavirin Combination Therapy.** by Veillon P, Payan C, Picchio G, Maniez-Montreuil M, Guntz P, Lunel F.; 2003 Jul;
http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=165326
- **Comparative Evaluation of the VERSANT HCV RNA 3.0, QUANTIPLEX HCV RNA 2.0, and COBAS AMPLICOR HCV MONITOR Version 2.0 Assays for Quantification of Hepatitis C Virus RNA in Serum.** by Germer JJ, Heimgartner PJ, Ilstrup DM, Harmsen WS, Jenkins GD, Patel R.; 2002 Feb;
http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=153351
- **Comparative Sequence Analysis of the Core Protein and Its Frameshift Product, the F Protein, of Hepatitis C Virus Subtype 1b Strains Obtained from Patients with and without Hepatocellular Carcinoma.** by Ogata S, Nagano-Fujii M, Ku Y, Yoon S, Hotta H.; 2002 Oct;
http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=130847
- **Comparative study of three methods for genotyping hepatitis C virus strains in samples from Spanish patients.** by Forns X, Maluenda MD, Lopez-Labrador FX, Ampurdanes S, Olmedo E, Costa J, Simmonds P, Sanchez-Tapias JM, Jimenez De Anta MT, Rodes J.; 1996 Oct;
http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&rendertype=abstract&artid=229308
- **Comparison and Application of a Novel Genotyping Method, Semiautomated Primer-Specific and Mispair Extension Analysis, and Four Other Genotyping Assays for Detection of Hepatitis C Virus Mixed-Genotype Infections.** by Hu YW, Balaskas E, Furione M, Yen PH, Kessler G, Scalia V, Chui L, Sher G.; 2000 Aug;
http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=87116
- **Comparison of a competitive combined reverse transcription-PCR assay with a branched-DNA assay for hepatitis C virus RNA quantitation.** by Mayerat C, Burgisser P, Lavanchy D, Mantegani A, Frei PC.; 1996 Nov;
http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&rendertype=abstract&artid=229389
- **Comparison of DNA Enzyme Immunoassay and Line Probe Assays (Inno-LiPA HCV I and II) for Hepatitis C Virus Genotyping.** by Le Pogam S, Dubois F, Christen R, Raby C, Cavicchini A, Goudeau A.; 1998 May;
http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=104856
- **Comparison of full-length sequences of interferon-sensitive and resistant hepatitis C virus 1b. Sensitivity to interferon is conferred by amino acid substitutions in the NS5A region.** by Enomoto N, Sakuma I, Asahina Y, Kurosaki M, Murakami T, Yamamoto C, Izumi N, Marumo F, Sato C.; 1995 Jul;
http://www.pubmedcentral.gov/picrender.fcgi?tool=pmcentrez&action=stream&blobtype=pdf&artid=185192
- **Comparison of Hepatitis C Virus Genotyping by 5[prime prime or minute] Noncoding Region- and Core-Based Reverse Transcriptase PCR Assay with**

Sequencing and Use of the Assay for Determining Subtype Distribution in India. by Lole KS, Jha JA, Shrotri SP, Tandon BN, Prasad VG, Arankalle VA.; 2003 Nov; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=262521

- **Comparison of plasma virus loads among individuals infected with hepatitis C virus (HCV) genotypes 1, 2, and 3 by quantiplex HCV RNA assay versions 1 and 2, Roche Monitor assay, and an in-house limiting dilution method.** by Hawkins A, Davidson F, Simmonds P.; 1997 Jan; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&rendertype=abstract&artid=229536
- **Comparison of Serum Hepatitis C Virus RNA and Core Antigen Concentrations and Determination of Whether Levels Are Associated with Liver Histology or Affected by Specimen Storage Time.** by Lagging LM, Garcia CE, Westin J, Wejstal R, Norkrans G, Dhillon AP, Lindh M.; 2002 Nov; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=139660
- **Comparison of two quantitative hepatitis C virus reverse transcriptase PCR assays.** by Roth WK, Lee JH, Ruster B, Zeuzem S.; 1996 Feb; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&rendertype=abstract&artid=228779
- **Complement-Mediated Enhancement of Antibody Function for Neutralization of Pseudotype Virus Containing Hepatitis C Virus E2 Chimeric Glycoprotein.** by Meyer K, Basu A, Przysiecki CT, Lagging LM, Di Bisceglie AM, Conley AJ, Ray R.; 2002 Mar 1; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=153822
- **Concordance of hepatitis C virus typing methods based on restriction fragment length polymorphism analysis in 5' noncoding region and NS4 serotyping, but not in core PCR or a line probe assay.** by Navas S, Castillo I, Martin J, Quiroga JA, Bartolome J, Carreno V.; 1997 Jan; http://www.pubmedcentral.gov/picrender.fcgi?tool=pmcentrez&action=stream&blobtype=pdf&artid=229569
- **Confirmation of Nosocomial Transmission of Hepatitis C Virus by Phylogenetic Analysis of the NS5-B Region.** by Norder H, Bergstrom A, Uhnoo I, Alden J, Weiss L, Czajkowski J, Magnius L.; 1998 Oct; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=105115
- **Conservation of the Conformation and Positive Charges of Hepatitis C Virus E2 Envelope Glycoprotein Hypervariable Region 1 Points to a Role in Cell Attachment.** by Penin F, Combet C, Germanidis G, Frainais PO, Deleage G, Pawlotsky JM.; 2001 Jun 15; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=114285
- **Conserved C-Terminal Threonine of Hepatitis C Virus NS3 Regulates Autoproteolysis and Prevents Product Inhibition.** by Wang W, Lahser FC, Yi M, Wright-Minogue J, Xia E, Weber PC, Lemon SM, Malcolm BA.; 2004 Jan 15; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=368748
- **Control of Heterologous Hepatitis C Virus Infection in Chimpanzees Is Associated with the Quality of Vaccine-Induced Peripheral T-Helper Immune Response.** by Rollier C, Depla E, Drexhage JA, Verschoor EJ, Verstrepen BE, Fatmi A, Brinster C, Fournillier A, Whelan JA, Whelan M, Jacobs D, Maertens G, Inchauspe G, Heeney JL.; 2004 Jan 1; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=303385

- **Control of PKR Protein Kinase by Hepatitis C Virus Nonstructural 5A Protein: Molecular Mechanisms of Kinase Regulation.** by Gale M Jr, Blakely CM, Kwieciszewski B, Tan SL, Dossett M, Tang NM, Korth MJ, Polyak SJ, Gretch DR, Katze MG.; 1998 Sep;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=109106
- **Cooperative Oligonucleotides Mediating Direct Capture of Hepatitis C Virus RNA from Serum.** by O'Meara D, Yun Z, Sonnerborg A, Lundeberg J.; 1998 Sep;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=105143
- **Correlation between Mutations in the Interferon Sensitivity-Determining Region of NS5A Protein and Viral Load of Hepatitis C Virus Subtypes 1b, 1c, and 2a.** by Lusida MI, Nagano-Fujii M, Nidom CA, Soetjipto, Handajani R, Fujita T, Oka K, Hotta H.; 2001 Nov;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=88455
- **Correlation of serum antibody titers against hepatitis C virus core protein with clinical features by western blot (immunoblot) analysis using a recombinant vaccinia virus expression system.** by Nishizono A, Hiraga M, Mifune K, Terao H, Fujioka T, Nasu M, Goto T, Misumi J, Moriyama M, Arakawa Y, et al.; 1993 May;
  http://www.pubmedcentral.gov/picrender.fcgi?tool=pmcentrez&action=stream&blobtype=pdf&artid=262898
- **Cross-Reactivity between Hepatitis C Virus and Influenza A Virus Determinant-Specific Cytotoxic T Cells.** by Wedemeyer H, Mizukoshi E, Davis AR, Bennink JR, Rehermann B.; 2001 Dec 1;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=114725
- **Cytopathic and Noncytopathic Interferon Responses in Cells Expressing Hepatitis C Virus Subgenomic Replicons.** by Guo JT, Zhu Q, Seeger C.; 2003 Oct 15;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=224980
- **Cytoskeletal Requirements for Hepatitis C Virus (HCV) RNA Synthesis in the HCV Replicon Cell Culture System.** by Bost AG, Venable D, Liu L, Heinz BA.; 2003 Apr 1;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=150619
- **De Novo Initiation of RNA Synthesis by Hepatitis C Virus Nonstructural Protein 5B Polymerase.** by Zhong W, Uss AS, Ferrari E, Lau JY, Hong Z.; 2000 Feb 15;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=111680
- **Decreased Frequency of the HLA-DRB1*11 Allele in Patients with Chronic Hepatitis C Virus Infection.** by Yenigun A, Durupinar B.; 2002 Feb 15;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=135873
- **Detection and Analysis of Hepatitis C Virus Sequences in Cerebrospinal Fluid.** by Laskus T, Radkowski M, Bednarska A, Wilkinson J, Adair D, Nowicki M, Nikolopoulou GB, Vargas H, Rakela J.; 2002 Oct 1;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=136534
- **Detection and Characterization of Hepatitis C Virus RNA in Seminal Plasma and Spermatozoon Fractions of Semen from Patients Attempting Medically Assisted Conception.** by Bourlet T, Levy R, Maertens A, Tardy JC, Grattard F, Cordonier H, Laurent JL, Guerin JF, Pozzetto B.; 2002 Sep;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=130669

- **Detection and Quantitation of Hepatitis C Virus RNA in Feces of Chronically Infected Individuals.** by Beld M, Sentjens R, Rebers S, Weel J, Wertheim-van Dillen P, Sol C, Boom R.; 2000 Sep;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=87401
- **Detection of a Novel Unglycosylated Form of Hepatitis C Virus E2 Envelope Protein That Is Located in the Cytosol and Interacts with PKR.** by Pavio N, Taylor DR, Lai MM.; 2002 Feb 1;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=135859
- **Detection of antibodies to hepatitis C virus (HCV) structural proteins in anti-HCV-positive sera by an enzyme-linked immunosorbent assay using synthetic peptides as antigens.** by Ishida C, Matsumoto K, Fukada K, Matsushita K, Shiraki H, Maeda Y.; 1993 Apr;
  http://www.pubmedcentral.gov/picrender.fcgi?tool=pmcentrez&action=stream&blobtype=pdf&artid=263590
- **Detection of Diverse Hepatitis C Virus (HCV)-Specific Cytotoxic T Lymphocytes in Peripheral Blood of Infected Persons by Screening for Responses to All Translated Proteins of HCV.** by Wong DK, Dudley DD, Dohrenwend PB, Lauer GM, Chung RT, Thomas DL, Walker BD.; 2001 Feb 1;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=114029
- **Detection of genomic and intermediate replicative strands of hepatitis C virus in liver tissue by in situ hybridization.** by Nouri Aria KT, Sallie R, Sangar D, Alexander GJ, Smith H, Byrne J, Portmann B, Eddleston AL, Williams R.; 1993 May;
  http://www.pubmedcentral.gov/picrender.fcgi?tool=pmcentrez&action=stream&blobtype=pdf&artid=288225
- **Detection of hepatitis C virus RNA by a combined reverse transcription PCR assay: comparison with nested amplification and antibody testing.** by Young KK, Archer JJ, Yokosuka O, Omata M, Resnick RM.; 1995 Mar;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&rendertype=abstract&artid=228008
- **Detection of hepatitis C virus RNA by a combined reverse transcription-polymerase chain reaction assay.** by Young KK, Resnick RM, Myers TW.; 1993 Apr;
  http://www.pubmedcentral.gov/picrender.fcgi?tool=pmcentrez&action=stream&blobtype=pdf&artid=263581
- **Detection of hepatitis C virus sequences in sera with controversial serology by nested polymerase chain reaction.** by Lazizi Y, Elfassi E, Pillot J.; 1992 Apr;
  http://www.pubmedcentral.gov/picrender.fcgi?tool=pmcentrez&action=stream&blobtype=pdf&artid=265188
- **Detection of intrahepatic replication of hepatitis C virus RNA by in situ hybridization and comparison with histopathology.** by Negro F, Pacchioni D, Shimizu Y, Miller RH, Bussolati G, Purcell RH, Bonino F.; 1992 Mar 15;
  http://www.pubmedcentral.gov/picrender.fcgi?tool=pmcentrez&action=stream&blobtype=pdf&artid=48634
- **Detection of the hepatitis C virus genome in acute and chronic experimental infection in chimpanzees.** by Schlauder GG, Leverenz GJ, Amann CW, Lesniewski RR, Peterson DA.; 1991 Oct;
  http://www.pubmedcentral.gov/picrender.fcgi?tool=pmcentrez&action=stream&blobtype=pdf&artid=270293

- **Detection, semiquantitation, and genetic variation in hepatitis C virus sequences amplified from the plasma of blood donors with elevated alanine aminotransferase.** by Ulrich PP, Romeo JM, Lane PK, Kelly I, Daniel LJ, Vyas GN.; 1990 Nov; http://www.pubmedcentral.gov/picrender.fcgi?tool=pmcentrez&action=stream&blobtype=pdf&artid=296910
- **Determination of genotypes of hepatitis C virus in Venezuela by restriction fragment length polymorphism.** by Pujol FH, Loureiro CL, Devesa M, Blitz L, Parra K, Beker S, Liprandi F.; 1997 Jul; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&rendertype=abstract&artid=229860
- **Determination of Hepatitis C Virus Genotype by Direct Sequence Analysis of Products Generated with the Amplicor HCV Test.** by Germer JJ, Rys PN, Thorvilson JN, Persing DH.; 1999 Aug; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=85299
- **Determination of hepatitis C virus genotypes in the United States by cleavase fragment length polymorphism analysis.** by Marshall DJ, Heisler LM, Lyamichev V, Murvine C, Olive DM, Ehrlich GD, Neri BP, de Arruda M.; 1997 Dec; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&rendertype=abstract&artid=230140
- **Determination of the secondary structure of and cellular protein binding to the 3'-untranslated region of the hepatitis C virus RNA genome.** by Ito T, Lai MM.; 1997 Nov; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&rendertype=abstract&artid=192334
- **Development of a Simple and Highly Sensitive Enzyme Immunoassay for Hepatitis C Virus Core Antigen.** by Aoyagi K, Ohue C, Iida K, Kimura T, Tanaka E, Kiyosawa K, Yagi S.; 1999 Jun; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=84955
- **Different Hepatitis C Virus (HCV) RNA Load Profiles Following Seroconversion among Injecting Drug Users without Correlation with HCV Genotype and Serum Alanine Aminotransferase Levels.** by Beld M, Penning M, McMorrow M, Gorgels J, van den Hoek A, Goudsmit J.; 1998 Apr; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=104653
- **Differential prevalence of hepatitis C virus subtypes in healthy blood donors, patients on maintenance hemodialysis, and patients with hepatocellular carcinoma in Surabaya, Indonesia.** by Soetjipto, Handajani R, Lusida MI, Darmadi S, Adi P, Soemarto, Ishido S, Katayama Y, Hotta H.; 1996 Dec; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&rendertype=abstract&artid=229426
- **Direct detection of circulating hepatitis C virus RNA using probes from the 5' untranslated region.** by Hu KQ, Yu CH, Vierling JM.; 1992 Jun; http://www.pubmedcentral.gov/picrender.fcgi?tool=pmcentrez&action=stream&blobtype=pdf&artid=295919

- **Discordant results from hepatitis C virus genotyping by procedures based on amplification of different genomic regions.** by Toniutto P, Pirisi M, Tisminetzky SG, Fabris C, Chinellato E, Gerotto M, Falleti E, Ferroni P, Lombardelli T, Bartoli E, Baralle F.; 1996 Oct;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&rendertype=abstract&artid=229274
- **Distribution of viral genotypes in Italy determined by hepatitis C virus typing by DNA immunoassay.** by Ravaggi A, Zonaro A, Marin MG, Puoti M, Albertini A, Cariani E.; 1994 Sep;
  http://www.pubmedcentral.gov/picrender.fcgi?tool=pmcentrez&action=stream&blobtype=pdf&artid=263983
- **Diverse patterns of recognition of hepatitis C virus core and nonstructural antigens by antibodies present in Egyptian cancer patients and blood donors.** by Attia MA, Zekri AR, Goudsmit J, Boom R, Khaled HM, Mansour MT, de Wolf F, el-Din HM, Sol CJ.; 1996 Nov;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&rendertype=abstract&artid=229382
- **Diversity of Hepatitis C Virus Quasispecies Evaluated by Denaturing Gradient Gel Electrophoresis.** by Harris KA, Teo CG.; 2001 Jan;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=96012
- **DNA Immunization with Hepatitis C Virus (HCV) Polycistronic Genes or Immunization by HCV DNA Priming-Recombinant Canarypox Virus Boosting Induces Immune Responses and Protection from Recombinant HCV-Vaccinia Virus Infection in HLA-A2.1-Transgenic Mice.** by Pancholi P, Perkus M, Tricoche N, Liu Q, Prince AM.; 2003 Jan 1;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=140575
- **DNA Microarray Analysis of Chimpanzee Liver during Acute Resolving Hepatitis C Virus Infection.** by Bigger CB, Brasky KM, Lanford RE.; 2001 Aug 1;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=114434
- **Dominant Role of Host Selective Pressure in Driving Hepatitis C Virus Evolution in Perinatal Infection.** by Manzin A, Solforosi L, Debiaggi M, Zara F, Tanzi E, Romano L, Zanetti AR, Clementi M.; 2000 May 1;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=111950
- **Dynamic analysis of heterogeneous hepatitis C virus populations by direct solid-phase sequencing.** by Odeberg J, Yun Z, Sonnerborg A, Uhlen M, Lundeberg J.; 1995 Jul;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&rendertype=abstract&artid=228288
- **Dynamics of Persistent TT Virus Infection, as Determined in Patients Treated with Alpha Interferon for Concomitant Hepatitis C Virus Infection.** by Maggi F, Pistello M, Vatteroni M, Presciuttini S, Marchi S, Isola P, Fornai C, Fagnani S, Andreoli E, Antonelli G, Bendinelli M.; 2001 Dec 15;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=116095
- **Dynamics of Subgenomic Hepatitis C Virus Replicon RNA Levels in Huh-7 Cells after Exposure to Nucleoside Antimetabolites.** by Stuyver LJ, McBrayer TR, Tharnish PM, Hassan AE, Chu CK, Pankiewicz KW, Watanabe KA, Schinazi RF, Otto MJ.; 2003 Oct 1;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=228517

- **Ectopic Expression of Hepatitis C Virus Core Protein Differentially Regulates Nuclear Transcription Factors.** by Shrivastava A, Manna SK, Ray R, Aggarwal BB.; 1998 Dec;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=110482
- **Effect of Alpha Interferon on the Hepatitis C Virus Replicon.** by Guo JT, Bichko VV, Seeger C.; 2001 Sep 15;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=115097
- **Effect of Multiple Freeze-Thaw Cycles on Hepatitis B Virus DNA and Hepatitis C Virus RNA Quantification as Measured with Branched-DNA Technology.** by Krajden M, Minor JM, Rifkin O, Comanor L.; 1999 Jun;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=84922
- **Effect of Retreatment with Interferon Alone or Interferon plus Ribavirin on Hepatitis C Virus Quasispecies Diversification in Nonresponder Patients with Chronic Hepatitis C.** by Gerotto M, Sullivan DG, Polyak SJ, Chemello L, Cavalletto L, Pontisso P, Alberti A, Gretch DR.; 1999 Sep;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=104248
- **Effects of Storage and Type of Blood Collection Tubes on Hepatitis C Virus Level in Whole Blood Samples.** by Kessler HH, Stelzl E, Raggam RB, Haas J, Kirchmeir F, Hegenbarth K, Daghofer E, Santner BI, Marth E, Stauber RE.; 2001 May;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=88026
- **Efficient Replication of Hepatitis C Virus Genotype 1a RNAs in Cell Culture.** by Blight KJ, McKeating JA, Marcotrigiano J, Rice CM.; 2003 Mar 1;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=149761
- **Enhanced amplification of hepatitis C virus (HCV) cDNA by PCR: detection of HCV RNA in archival sera.** by Beardsley AM, Gowans EJ, Burrell CJ, Marmion BP.; 1996 Jun;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&rendertype=abstract&artid=229070
- **Enhancement of Hepatitis C Virus RNA Replication by Cell Culture-Adaptive Mutations.** by Krieger N, Lohmann V, Bartenschlager R.; 2001 May 15;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=114214
- **Enhancement of Immunoglobulin G2a and Cytotoxic T-Lymphocyte Responses by a Booster Immunization with Recombinant Hepatitis C Virus E2 Protein in E2 DNA-Primed Mice.** by Song MK, Lee SW, Suh YS, Lee KJ, Sung YC.; 2000 Mar 15;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=111786
- **Enhancing B- and T-Cell Immune Response to a Hepatitis C Virus E2 DNA Vaccine by Intramuscular Electrical Gene Transfer.** by Zucchelli S, Capone S, Fattori E, Folgori A, Di Marco A, Casimiro D, Simon AJ, Laufer R, La Monica N, Cortese R, Nicosia A.; 2000 Dec 15;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=112441
- **Enzymatic characterization of hepatitis C virus NS3/4A complexes expressed in mammalian cells by using the herpes simplex virus amplicon system.** by Hong Z, Ferrari E, Wright-Minogue J, Chase R, Risano C, Seelig G, Lee CG, Kwong AD.; 1996 Jul;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&rendertype=abstract&artid=190357

- **Epidemiological Dynamics of Hepatitis C Virus among 747 German Individuals: New Subtypes on the Advance.** by Schroter M, Zollner B, Schafer P, Reimer A, Muller M, Laufs R, Feucht HH.; 2002 May;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=130918
- **Evaluation of Accumulation of Hepatitis C Virus Mutations in a Chronically Infected Chimpanzee: Comparison of the Core, E1, HVR1, and NS5b Regions.** by Lu L, Nakano T, Orito E, Mizokami M, Robertson BH.; 2001 Mar 15;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=115927
- **Evaluation of the MagNA Pure LC Instrument for Extraction of Hepatitis C Virus RNA for the COBAS AMPLICOR Hepatitis C Virus Test, Version 2.0.** by Germer JJ, Lins MM, Jensen ME, Harmsen WS, Ilstrup DM, Mitchell PS, Cockerill III FR, Patel R.; 2003 Aug;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=179864
- **Evaluation of the TRUGENE HCV 5[prime prime or minute]NC Genotyping Kit with the New GeneLibrarian Module 3.1.2 for Genotyping of Hepatitis C Virus from Clinical Specimens.** by Germer JJ, Majewski DW, Rosser M, Thompson A, Mitchell PS, Smith TF, Elagin S, Yao JD.; 2003 Oct;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=254363
- **Evaluation of the VERSANT HCV RNA 3.0 Assay for Quantification of Hepatitis C Virus RNA in Serum.** by Trimoulet P, Halfon P, Pohier E, Khiri H, Chene G, Fleury H.; 2002 Jun;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=130754
- **Evidence for immune selection of hepatitis C virus (HCV) putative envelope glycoprotein variants: potential role in chronic HCV infections.** by Weiner AJ, Geysen HM, Christopherson C, Hall JE, Mason TJ, Saracco G, Bonino F, Crawford K, Marion CD, Crawford KA, et al.; 1992 Apr 15;
  http://www.pubmedcentral.gov/picrender.fcgi?tool=pmcentrez&action=stream&blobtype=pdf&artid=48889
- **Evidence of subtype-specific antibodies to antigenic epitopes in the NS5 region of hepatitis C virus in the circulation of patients with chronic hepatitis C.** by Quiroga JA, Martin J, Pernas M, Pardo M, Herrero M, Castillo I, Bartolome J, Carreno V.; 1994 Sep;
  http://www.pubmedcentral.gov/picrender.fcgi?tool=pmcentrez&action=stream&blobtype=pdf&artid=368335
- **Evolution of Hepatitis C Virus Quasispecies in Hypervariable Region 1 and the Putative Interferon Sensitivity-Determining Region during Interferon Therapy and Natural Infection.** by Polyak SJ, McArdle S, Liu SL, Sullivan DG, Chung M, Hofgartner WT, Carithers RL Jr, McMahon BJ, Mullins JI, Corey L, Gretch DR.; 1998 May;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=109659
- **Evolution of Hypervariable Region 1 of Hepatitis C Virus in Primary Infection.** by Manzin A, Solforosi L, Petrelli E, Macarri G, Tosone G, Piazza M, Clementi M.; 1998 Jul;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=110460
- **Evolution of the Hepatitis C Virus Second Envelope Protein Hypervariable Region in Chronically Infected Patients Receiving Alpha Interferon Therapy.** by Pawlotsky JM, Germanidis G, Frainais PO, Bouvier M, Soulier A, Pellerin M, Dhumeaux D.; 1999 Aug;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=112731

- **Evolutionary Rate and Genetic Drift of Hepatitis C Virus Are Not Correlated with the Host Immune Response: Studies of Infected Donor-Recipient Clusters.** by Allain JP, Dong Y, Vandamme AM, Moulton V, Salemi M.; 2000 Mar 15; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=111742
- **Ex vivo analysis of human memory CD4 T cells specific for hepatitis C virus using MHC class II tetramers.** by Day CL, Seth NP, Lucas M, Appel H, Gauthier L, Lauer GM, Robbins GK, Szczepiorkowski ZM, Casson DR, Chung RT, Bell S, Harcourt G, Walker BD, Klenerman P, Wucherpfennig KW.; 2003 Sep 15; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=193667
- **Existence of Hepatitis C Virus in Culex quinquefasciatus after Ingestion of Infected Blood: Experimental Approach to Evaluating Transmission by Mosquitoes.** by Chang TT, Chang TY, Chen CC, Young KC, Roan JN, Lee YC, Cheng PN, Wu HL.; 2001 Sep; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=88344
- **Exposure of Hepatitis C Virus (HCV) RNA-Positive Recipients to HCV RNA-Positive Blood Donors Results in Rapid Predominance of a Single Donor Strain and Exclusion and/or Suppression of the Recipient Strain.** by Laskus T, Wang LF, Radkowski M, Vargas H, Nowicki M, Wilkinson J, Rakela J.; 2001 Mar 1; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=114790
- **Expression of Hepatitis C Virus Proteins Induces Distinct Membrane Alterations Including a Candidate Viral Replication Complex.** by Egger D, Wolk B, Gosert R, Bianchi L, Blum HE, Moradpour D, Bienz K.; 2002 Jun 15; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=136238
- **Expression of Hepatitis C Virus Proteins Inhibits Signal Transduction through the Jak-STAT Pathway.** by Heim MH, Moradpour D, Blum HE.; 1999 Oct; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=112866
- **Expression of Hepatitis C Virus Proteins Interferes with the Antiviral Action of Interferon Independently of PKR-Mediated Control of Protein Synthesis.** by Francois C, Duverlie G, Rebouillat D, Khorsi H, Castelain S, Blum HE, Gatignol A, Wychowski C, Moradpour D, Meurs EF.; 2000 Jun 15; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=112046
- **Expression of Noncovalent Hepatitis C Virus Envelope E1-E2 Complexes Is Not Required for the Induction of Antibodies with Neutralizing Properties following DNA Immunization.** by Fournillier A, Depla E, Karayiannis P, Vidalin O, Maertens G, Trepo C, Inchauspe G.; 1999 Sep; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=104276
- **Expression of processed core protein of hepatitis C virus in mammalian cells.** by Harada S, Watanabe Y, Takeuchi K, Suzuki T, Katayama T, Takebe Y, Saito I, Miyamura T.; 1991 Jun; http://www.pubmedcentral.gov/picrender.fcgi?tool=pmcentrez&action=stream&blobtype=pdf&artid=240954
- **Expression of processed envelope protein of hepatitis C virus in mammalian and insect cells.** by Matsuura Y, Harada S, Suzuki R, Watanabe Y, Inoue Y, Saito I, Miyamura T.; 1992 Mar; http://www.pubmedcentral.gov/picrender.fcgi?tool=pmcentrez&action=stream&blobtype=pdf&artid=240866
- **Expression of Unmodified Hepatitis C Virus Envelope Glycoprotein-Coding Sequences Leads to Cryptic Intron Excision and Cell Surface Expression of E1/E2**

Heterodimers Comprising Full-Length and Partially Deleted E1. by Dumonceaux J, Cormier EG, Kajumo F, Donovan GP, Roy-Chowdhury J, Fox IJ, Gardner JP, Dragic T.; 2003 Dec 15;
http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=296095

- **External Quality Assessment Program for Qualitative and Quantitative Detection of Hepatitis C Virus RNA in Diagnostic Virology.** by Schirm J, van Loon AM, Valentine-Thon E, Klapper PE, Reid J, Cleator GM.; 2002 Aug;
http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=120662
- **Formation and intracellular localization of hepatitis C virus envelope glycoprotein complexes expressed by recombinant vaccinia and Sindbis viruses.** by Dubuisson J, Hsu HH, Cheung RC, Greenberg HB, Russell DG, Rice CM.; 1994 Oct;
http://www.pubmedcentral.gov/picrender.fcgi?tool=pmcentrez&action=stream&blobtype=pdf&artid=237034
- **Formation of native hepatitis C virus glycoprotein complexes.** by Deleersnyder V, Pillez A, Wychowski C, Blight K, Xu J, Hahn YS, Rice CM, Dubuisson J.; 1997 Jan;
http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&rendertype=abstract&artid=191102
- **Frequent Recovery and Broad Genotype 2 Diversity Characterize Hepatitis C Virus Infection in Ghana, West Africa.** by Candotti D, Temple J, Sarkodie F, Allain JP.; 2003 Jul 15;
http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=161936
- **Functional Characterization of Intracellular and Secreted Forms of a Truncated Hepatitis C Virus E2 Glycoprotein.** by Flint M, Dubuisson J, Maidens C, Harrop R, Guile GR, Borrow P, McKeating JA.; 2000 Jan 15;
http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=111590
- **Functional Measurement of Hepatitis C Virus Core-Specific CD8 + T-Cell Responses in the Livers or Peripheral Blood of Patients by Using Autologous Peripheral Blood Mononuclear Cells as Targets or Stimulators.** by Fang SH, Chiang BL, Wu MH, Iba H, Lai MY, Yang PM, Chen DS, Hwang LH.; 2001 Nov;
http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=88461
- **Functional Role of Hepatitis C Virus Chimeric Glycoproteins in the Infectivity of Pseudotyped Virus.** by Lagging LM, Meyer K, Owens RJ, Ray R.; 1998 May;
http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=109573
- **Gene Expression Profiling of the Cellular Transcriptional Network Regulated by Alpha/Beta Interferon and Its Partial Attenuation by the Hepatitis C Virus Nonstructural 5A Protein.** by Geiss GK, Carter VS, He Y, Kwieciszewski BK, Holzman T, Korth MJ, Lazaro CA, Fausto N, Bumgarner RE, Katze MG.; 2003 Jun 1;
http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=155033
- **Genetic Analysis of Sequences in the 3[prime prime or minute] Nontranslated Region of Hepatitis C Virus That Are Important for RNA Replication.** by Friebe P, Bartenschlager R.; 2002 Jun 1;
http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=137049
- **Genetic and Serological Evidence for Multiple Instances of Unrecognized Transmission of Hepatitis C Virus in Hemodialysis Units.** by Mizuno M, Higuchi T, Kanmatsuse K, Esumi M.; 1998 Oct;
http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=105089

- **Genetic Clustering of Hepatitis C Virus Strains and Severity of Recurrent Hepatitis after Liver Transplantation.** by Gigou M, Roque-Afonso AM, Falissard B, Penin F, Dussaix E, Feray C.; 2001 Dec 1;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=114714
- **Genetic Diversity and Tissue Compartmentalization of the Hepatitis C Virus Genome in Blood Mononuclear Cells, Liver, and Serum from Chronic Hepatitis C Patients.** by Navas S, Martin J, Quiroga JA, Castillo I, Carreno V.; 1998 Feb;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=124648
- **Genetic Heterogeneity of Hypervariable Region 1 of the Hepatitis C Virus (HCV) Genome and Sensitivity of HCV to Alpha Interferon Therapy.** by Sandres K, Dubois M, Pasquier C, Payen JL, Alric L, Duffaut M, Vinel JP, Pascal JP, Puel J, Izopet J.; 2000 Jan 15;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=111585
- **Genetic Immunization of Wild-Type and Hepatitis C Virus Transgenic Mice Reveals a Hierarchy of Cellular Immune Response and Tolerance Induction against Hepatitis C Virus Structural Proteins.** by Satoi J, Murata K, Lechmann M, Manickan E, Zhang Z, Wedemeyer H, Rehermann B, Liang TJ.; 2001 Dec 15;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=116108
- **Genomic analysis of the host response to hepatitis C virus infection.** by Su AI, Pezacki JP, Wodicka L, Brideau AD, Supekova L, Thimme R, Wieland S, Bukh J, Purcell RH, Schultz PG, Chisari FV.; 2002 Nov 26;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=137774
- **Genomic and Phylogenetic Analysis of Hepatitis C Virus Isolates from Argentine Patients: a Six-Year Retrospective Study.** by Quarleri JF, Robertson BH, Mathet VL, Feld M, Espinola L, Requeijo MP, Mando O, Carballal G, Oubina JR.; 2000 Dec;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=87637
- **Genotype dependence of hepatitis C virus antibodies detectable by the first-generation enzyme-linked immunosorbent assay with C100-3 protein.** by Nagayama R, Tsuda F, Okamoto H, Wang Y, Mitsui T, Tanaka T, Miyakawa Y, Mayumi M.; 1993 Sep;
  http://www.pubmedcentral.gov/picrender.fcgi?tool=pmcentrez&action=stream&blobtype=pdf&artid=288299
- **Genotype Dependence of Hepatitis C Virus Load Measurement in Commercially Available Quantitative Assays.** by Mellor J, Hawkins A, Simmonds P.; 1999 Aug;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=85273
- **Genotyping hepatitis C virus isolates from Spain, Brazil, China, and Macau by a simplified PCR method.** by Holland PV, Barrera JM, Ercilla MG, Yoshida CF, Wang Y, de Olim GA, Betlach B, Kuramoto K, Okamoto H.; 1996 Oct;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&rendertype=abstract&artid=229272
- **Genotyping of Canadian hepatitis C virus isolates by PCR.** by Andonov A, Chaudhary RK.; 1994 Aug;
  http://www.pubmedcentral.gov/picrender.fcgi?tool=pmcentrez&action=stream&blobtype=pdf&artid=263927

- **Genotyping of hepatitis C virus in South Africa.** by Smuts HE, Kannemeyer J.; 1995 Jun;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&rendertype=abstract&artid=228247
- **Genotyping of Hepatitis C Virus Isolates using CLIP Sequencing.** by Ross RS, Viazov SO, Holtzer CD, Beyou A, Monnet A, Mazure C, Roggendorf M.; 2000 Oct;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=87440
- **Genotyping of Hepatitis C Virus Types 1, 2, 3, and 4 by a One-Step LightCycler Method Using Three Different Pairs of Hybridization Probes.** by Schroter M, Zollner B, Schafer P, Landt O, Lass U, Laufs R, Feucht HH.; 2002 Jun;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=130695
- **Geographical distribution of hepatitis C virus genotypes in blood donors: an international collaborative survey.** by McOmish F, Yap PL, Dow BC, Follett EA, Seed C, Keller AJ, Cobain TJ, Krusius T, Kolho E, Naukkarinen R, et al.; 1994 Apr;
  http://www.pubmedcentral.gov/picrender.fcgi?tool=pmcentrez&action=stream&blobtype=pdf&artid=263157
- **Greater diversity of hepatitis C virus genotypes found in Hong Kong than in mainland China.** by Zhang YY, Lok AS, Chan DT, Widell A.; 1995 Nov;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&rendertype=abstract&artid=228609
- **Hepatitis B or Hepatitis C Virus Infection Is a Risk Factor for Severe Hepatic Cytolysis after Initiation of a Protease Inhibitor-Containing Antiretroviral Regimen in Human Immunodeficiency Virus-Infected Patients.** by Saves M, Raffi F, Clevenbergh P, Marchou B, Waldner-Combernoux A, Morlat P, Le Moing V, Riviere C, Chene G, Leport C.; 2000 Dec;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=90223
- **High incidence of hepatitis C virus infection in hemodialysis patients in units with high prevalence.** by Pujol FH, Ponce JG, Lema MG, Capriles F, Devesa M, Sirit F, Salazar M, Vasquez G, Monsalve F, Blitz-Dorfman L.; 1996 Jul;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&rendertype=abstract&artid=229084
- **Highly Permissive Cell Lines for Subgenomic and Genomic Hepatitis C Virus RNA Replication.** by Blight KJ, McKeating JA, Rice CM.; 2002 Dec 15;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=136668
- **Highly Sensitive Multiplex Assay for Detection of Human Immunodeficiency Virus Type 1 and Hepatitis C Virus RNA.** by Giachetti C, Linnen JM, Kolk DP, Dockter J, Gillotte-Taylor K, Park M, Ho-Sing-Loy M, McCormick MK, Mimms LT, McDonough SH.; 2002 Jul;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=120571
- **High-Throughput Real-Time Reverse Transcription-PCR Quantitation of Hepatitis C Virus RNA.** by Martell M, Gomez J, Esteban JI, Sauleda S, Quer J, Cabot B, Esteban R, Guardia J.; 1999 Feb;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=84298
- **HLA-Cw*04 and Hepatitis C Virus Persistence.** by Thio CL, Gao X, Goedert JJ, Vlahov D, Nelson KE, Hilgartner MW, O'Brien SJ, Karacki P, Astemborski J, Carrington M, Thomas DL.; 2002 May 15;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=136132

- **How Escherichia coli can bias the results of molecular cloning: Preferential selection of defective genomes of hepatitis C virus during the cloning procedure.** by Forns X, Bukh J, Purcell RH, Emerson SU.; 1997 Dec 9;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=28406
- **Human hepatitis C virus NS5A protein alters intracellular calcium levels, induces oxidative stress, and activates STAT-3 and NF-[kappa]B.** by Gong G, Waris G, Tanveer R, Siddiqui A.; 2001 Aug 14;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=55498
- **Human Immunodeficiency Virus Seroconversion and Evolution of the Hepatitis C Virus Quasispecies.** by Mao Q, Ray SC, Laeyendecker O, Ticehurst JR, Strathdee SA, Vlahov D, Thomas DL.; 2001 Apr 1;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=114119
- **Human Monoclonal Antibodies That Inhibit Binding of Hepatitis C Virus E2 Protein to CD81 and Recognize Conserved Conformational Epitopes.** by Hadlock KG, Lanford RE, Perkins S, Rowe J, Yang Q, Levy S, Pileri P, Abrignani S, Foung SK.; 2000 Nov 15;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=110915
- **Hyperphosphorylation of the Hepatitis C Virus NS5A Protein Requires an Active NS3 Protease, NS4A, NS4B, and NS5A Encoded on the Same Polyprotein.** by Neddermann P, Clementi A, De Francesco R.; 1999 Dec;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=113049
- **Hypervariable Region 1 Sequence Stability during Hepatitis C Virus Replication in Chimpanzees.** by Ray SC, Mao Q, Lanford RE, Bassett S, Laeyendecker O, Wang YM, Thomas DL.; 2000 Apr 1;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=111804
- **Identification of a C-Terminal Regulatory Motif in Hepatitis C Virus RNA-Dependent RNA Polymerase: Structural and Biochemical Analysis.** by Leveque VJ, Johnson RB, Parsons S, Ren J, Xie C, Zhang F, Wang QM.; 2003 Aug 15;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=167210
- **Identification of a Domain Containing B-Cell Epitopes in Hepatitis C Virus E2 Glycoprotein by Using Mouse Monoclonal Antibodies.** by Lee JW, Kim KM, Jung SH, Lee KJ, Choi EC, Sung YC, Kang CY.; 1999 Jan;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=103802
- **Identification of a Hepatic Factor Capable of Supporting Hepatitis C Virus Replication in a Nonpermissive Cell Line.** by Yeh CT, Lai HY, Chen TC, Chu CM, Liaw YF.; 2001 Nov 15;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=114682
- **Identification of Amino Acid Residues in CD81 Critical for Interaction with Hepatitis C Virus Envelope Glycoprotein E2.** by Higginbottom A, Quinn ER, Kuo CC, Flint M, Wilson LH, Bianchi E, Nicosia A, Monk PN, McKeating JA, Levy S.; 2000 Apr 15;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=111874
- **Identification of Hepatitis C Virus (HCV) Subtype 1b Strains That Are Highly, or Only Weakly, Associated with Hepatocellular Carcinoma on the Basis of the Secondary Structure of an Amino-Terminal Portion of the HCV NS3 Protein.** by Ogata S, Huab Florese R, Nagano-Fujii M, Hidajat R, Deng L, Ku Y, Yoon S, Saito T, Kawata S, Hotta H.; 2003 Jul;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=165328

- **Identification of numerous hepatitis C virus genotypes in Montreal, Canada.** by Bernier L, Willems B, Delage G, Murphy DG.; 1996 Nov; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&rendertype=abstract&artid=229409
- **Identification of the Hepatitis C Virus RNA Replication Complex in Huh-7 Cells Harboring Subgenomic Replicons.** by Gosert R, Egger D, Lohmann V, Bartenschlager R, Blum HE, Bienz K, Moradpour D.; 2003 May 1; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=153965
- **Immune responses to plasmid DNA encoding the hepatitis C virus core protein.** by Lagging LM, Meyer K, Hoft D, Houghton M, Belshe RB, Ray R.; 1995 Sep; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&rendertype=abstract&artid=189461
- **Immunization with plasmid DNA encoding hepatitis C virus envelope E2 antigenic domains induces antibodies whose immune reactivity is linked to the injection mode.** by Nakano I, Maertens G, Major ME, Vitvitski L, Dubuisson J, Fournillier A, De Martynoff G, Trepo C, Inchauspe G.; 1997 Sep; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&rendertype=abstract&artid=192006
- **Immunodominant regions within the hepatitis C virus core and putative matrix proteins.** by Sallberg M, Ruden U, Wahren B, Magnius LO.; 1992 Aug; http://www.pubmedcentral.gov/picrender.fcgi?tool=pmcentrez&action=stream&blobtype=pdf&artid=265429
- **Impact of Hepatitis B and Hepatitis C Virus Infections in a Hematology-Oncology Unit at a Children's Hospital in Nicaragua, 1997 to 1999.** by Visona K, Baez F, Taylor L, Berrios R, Leon B, Pacheco C, Jiron R, Luftig RB, Somarriba MM.; 2002 May; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=119972
- **Impact of Highly Active Antiretroviral Therapy and Immunologic Status on Hepatitis C Virus Quasispecies Diversity in Human Immunodeficiency Virus/Hepatitis C Virus-Coinfected Patients.** by Babik JM, Holodniy M.; 2003 Feb 1; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=140862
- **Improved reactivity of hepatitis C virus core protein epitopes in a conformational antigen-presenting system.** by Buratti E, Di Michele M, Song P, Monti-Bragadin C, Scodeller EA, Baralle FE, Tisminetzky SG.; 1997 Mar; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&rendertype=abstract&artid=170488
- **Improved Version 2.0 Qualitative and Quantitative AMPLICOR Reverse Transcription-PCR Tests for Hepatitis C Virus RNA: Calibration to International Units, Enhanced Genotype Reactivity, and Performance Characteristics.** by Lee SC, Antony A, Lee N, Leibow J, Yang JQ, Soviero S, Gutekunst K, Rosenstraus M.; 2000 Nov; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=87559
- **In Situ Distribution of Hepatitis C Virus Replicative-Intermediate RNA in Hepatic Tissue and Its Correlation with Liver Disease.** by Chang M, Marquardt AP, Wood BL, Williams O, Cotler SJ, Taylor SL, Carithers RL Jr, Gretch DR.; 2000 Jan 15; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=111615
- **In Vitro Detection of Dissimilar Amounts of Hepatitis C Virus (HCV) Subtype-Specific RNA Genomes in Mixes Prepared from Sera of Persons Infected with a**

Single HCV Genotype. by Quarleri JF, Bussy MV, Mathet VL, Ruiz V, Iacono R, Lu L, Robertson BH, Oubina JR.; 2003 Jun;
http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=156549

- **In vitro inhibition of hepatitis C virus gene expression by chemically modified antisense oligodeoxynucleotides.** by Vidalin O, Major ME, Rayner B, Imbach JL, Trepo C, Inchauspe G.; 1996 Oct;
http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&rendertype=abstract&artid=163531
- **In Vitro Selection and Characterization of Hepatitis C Virus Serine Protease Variants Resistant to an Active-Site Peptide Inhibitor.** by Trozzi C, Bartholomew L, Ceccacci A, Biasiol G, Pacini L, Altamura S, Narjes F, Muraglia E, Paonessa G, Koch U, De Francesco R, Steinkuhler C, Migliaccio G.; 2003 Mar 15;
http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=149541
- **In vivo analysis of the 3[prime prime or minute] untranslated region of the hepatitis C virus after in vitro mutagenesis of an infectious cDNA clone.** by Yanagi M, St. Claire M, Emerson SU, Purcell RH, Bukh J.; 1999 Mar 2;
http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=26776
- **Indeterminate results of the second-generation hepatitis C virus (HCV) recombinant immunoblot assay: significance of high-level c22-3 reactivity and influence of HCV genotypes.** by Zein NN, Germer JJ, Wendt NK, Schimek CM, Thorvilson JN, Mitchell PS, Persing DH.; 1997 Jan;
http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&rendertype=abstract&artid=229567
- **Influence of hepatitis C virus (HCV) genotypes on HCV recombinant immunoblot assay patterns.** by Pawlotsky JM, Roudot-Thoraval F, Pellet C, Aumont P, Darthuy F, Remire J, Duval J, Dhumeaux D.; 1995 May;
http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&rendertype=abstract&artid=228164
- **Inhibition of the Subgenomic Hepatitis C Virus Replicon in Huh-7 Cells by 2[prime prime or minute]-Deoxy-2[prime prime or minute]-Fluorocytidine.** by Stuyver LJ, McBrayer TR, Whitaker T, Tharnish PM, Ramesh M, Lostia S, Cartee L, Shi J, Hobbs A, Schinazi RF, Watanabe KA, Otto MJ.; 2004 Feb;
http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=321524
- **Interaction of Hepatitis C Virus Core Protein with Viral Sense RNA and Suppression of Its Translation.** by Shimoike T, Mimori S, Tani H, Matsuura Y, Miyamura T.; 1999 Dec;
http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=113018
- **Interaction of polypyrimidine tract-binding protein with the 5' noncoding region of the hepatitis C virus RNA genome and its functional requirement in internal initiation of translation.** by Ali N, Siddiqui A.; 1995 Oct;
http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&rendertype=abstract&artid=189536
- **Interaction with a Ubiquitin-Like Protein Enhances the Ubiquitination and Degradation of Hepatitis C Virus RNA-Dependent RNA Polymerase.** by Gao L, Tu H, Shi ST, Lee KJ, Asanaka M, Hwang SB, Lai MM.; 2003 Apr 1;
http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=150629

- **Interference of hepatitis C virus RNA replication by short interfering RNAs.** by Kapadia SB, Brideau-Andersen A, Chisari FV.; 2003 Feb 18; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=149950
- **Interferon Resistance of Hepatitis C Virus Genotype 1b: Relationship to Nonstructural 5A Gene Quasispecies Mutations.** by Pawlotsky JM, Germanidis G, Neumann AU, Pellerin M, Frainais PO, Dhumeaux D.; 1998 Apr; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=109724
- **Interleukin-1 Inhibits Hepatitis C Virus Subgenomic RNA Replication by Activation of Extracellular Regulated Kinase Pathway.** by Zhu H, Liu C.; 2003 May 1; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=153991
- **Internal ribosome entry site within hepatitis C virus RNA.** by Tsukiyama-Kohara K, Iizuka N, Kohara M, Nomoto A.; 1992 Mar; http://www.pubmedcentral.gov/picrender.fcgi?tool=pmcentrez&action=stream&blobtype=pdf&artid=240872
- **Intrahepatic Genetic Inoculation of Hepatitis C Virus RNA Confers Cross-Protective Immunity.** by Weiner AJ, Paliard X, Selby MJ, Medina-Selby A, Coit D, Nguyen S, Kansopon J, Arian CL, Ng P, Tucker J, Lee CT, Polakos NK, Han J, Wong S, Lu HH, Rosenberg S, Brasky KM, Chien D, Kuo G, Houghton M.; 2001 Aug 1; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=114443
- **Investigation of sera reactive to hepatitis C virus by second-generation enzyme immunoassay.** by Frost EH.; 1993 Jan; http://www.pubmedcentral.gov/picrender.fcgi?tool=pmcentrez&action=stream&blobtype=pdf&artid=262645
- **Involvement of Endoplasmic Reticulum Chaperones in the Folding of Hepatitis C Virus Glycoproteins.** by Choukhi A, Ung S, Wychowski C, Dubuisson J.; 1998 May; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=109609
- **Involvement of Proteasome [alpha]-Subunit PSMA7 in Hepatitis C Virus Internal Ribosome Entry Site-Mediated Translation.** by Kruger M, Beger C, Welch PJ, Barber JR, Manns MP, Wong-Staal F.; 2001 Dec 15; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=100000
- **Isolation and Characterization of Monoclonal Antibodies That Inhibit Hepatitis C Virus NS3 Protease.** by Ueno T, Misawa S, Ohba Y, Matsumoto M, Mizunuma M, Kasai N, Tsumoto K, Kumagai I, Hayashi H.; 2000 Jul 15; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=112135
- **Isolation of hepatitis C virus RNA from serum for reverse transcription-PCR.** by Nolte FS, Thurmond C, Mitchell PS.; 1994 Feb; http://www.pubmedcentral.gov/picrender.fcgi?tool=pmcentrez&action=stream&blobtype=pdf&artid=263065
- **Kinetic and structural analyses of hepatitis C virus polyprotein processing.** by Bartenschlager R, Ahlborn-Laake L, Mous J, Jacobsen H.; 1994 Aug; http://www.pubmedcentral.gov/picrender.fcgi?tool=pmcentrez&action=stream&blobtype=pdf&artid=236447
- **Kinetics of CD4 + and CD8 + Memory T-Cell Responses during Hepatitis C Virus Rechallenge of Previously Recovered Chimpanzees.** by Nascimbeni M, Mizukoshi E, Bosmann M, Major ME, Mihalik K, Rice CM, Feinstone SM, Rehermann B.; 2003 Apr 15; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=152131

- **Laboratory Assays for Diagnosis and Management of Hepatitis C Virus Infection.** by Richter SS.; 2002 Dec;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=154655
- **Lack of detection of negative-strand hepatitis C virus RNA in peripheral blood mononuclear cells and other extrahepatic tissues by the highly strand-specific rTth reverse transcriptase PCR.** by Lanford RE, Chavez D, Chisari FV, Sureau C.; 1995 Dec;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&rendertype=abstract&artid=189758
- **Levels of hepatitis C virus (HCV) RNA in serum and their relationship to levels of immunoglobulin M and G antibodies against HCV core protein.** by Chen M, Sonnerborg A, Sallberg M.; 1995 Mar;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&rendertype=abstract&artid=228037
- **Longitudinal Evaluation of the Structure of Replicating and Circulating Hepatitis C Virus Quasispecies in Nonprogressive Chronic Hepatitis C Patients.** by Cabot B, Martell M, Esteban JI, Piron M, Otero T, Esteban R, Guardia J, Gomez J.; 2001 Dec 15;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=116096
- **Long-Term Evolution of the Hypervariable Region of Hepatitis C Virus in a Common-Source-Infected Cohort.** by McAllister J, Casino C, Davidson F, Power J, Lawlor E, Yap PL, Simmonds P, Smith DB.; 1998 Jun;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=110045
- **Mapping B-Cell Epitopes of Hepatitis C Virus E2 Glycoprotein Using Human Monoclonal Antibodies from Phage Display Libraries.** by Bugli F, Mancini N, Kang CY, Di Campli C, Grieco A, Manzin A, Gabrielli A, Gasbarrini A, Fadda G, Varaldo PE, Clementi M, Burioni R.; 2001 Oct 15;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=114571
- **Mapping of serotype-specific, immunodominant epitopes in the NS-4 region of hepatitis C virus (HCV): use of type-specific peptides to serologically differentiate infections with HCV types 1, 2, and 3.** by Simmonds P, Rose KA, Graham S, Chan SW, McOmish F, Dow BC, Follett EA, Yap PL, Marsden H.; 1993 Jun;
  http://www.pubmedcentral.gov/picrender.fcgi?tool=pmcentrez&action=stream&blobtype=pdf&artid=265567
- **Mechanism of Action and Antiviral Activity of Benzimidazole-Based Allosteric Inhibitors of the Hepatitis C Virus RNA-Dependent RNA Polymerase.** by Tomei L, Altamura S, Bartholomew L, Biroccio A, Ceccacci A, Pacini L, Narjes F, Gennari N, Bisbocci M, Incitti I, Orsatti L, Harper S, Stansfield I, Rowley M, De Francesco R, Migliaccio G.; 2003 Dec 15;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=296079
- **Mistyping of two Slovenian hepatitis C virus subtype 2c isolates as subtype 2b by two 5' noncoding region genotyping methods.** by Seme K, Poljak M, Koren S, Dovc P.; 1997 Dec;
  http://www.pubmedcentral.gov/picrender.fcgi?tool=pmcentrez&action=stream&blobtype=pdf&artid=230194
- **Modulation of Hepatitis C Virus NS5A Hyperphosphorylation by Nonstructural Proteins NS3, NS4A, and NS4B.** by Oliver Koch J, Bartenschlager R.; 1999 Sep;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=104237

- **Molecular and Immunological Significance of Chimpanzee Major Histocompatibility Complex Haplotypes for Hepatitis C Virus Immune Response and Vaccination Studies.** by Mizukoshi E, Nascimbeni M, Blaustein JB, Mihalik K, Rice CM, Liang TJ, Feinstone SM, Rehermann B.; 2002 Jun 15; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=136197
- **Molecular cloning of the human hepatitis C virus genome from Japanese patients with non-A, non-B hepatitis.** by Kato N, Hijikata M, Ootsuyama Y, Nakagawa M, Ohkoshi S, Sugimura T, Shimotohno K.; 1990 Dec; http://www.pubmedcentral.gov/picrender.fcgi?tool=pmcentrez&action=stream&blobtype=pdf&artid=55204
- **Molecular Epidemiology of Hepatitis C Virus Infection in an Area of Hyperendemicity in Southern Italy: a Population-Based Study.** by Osella AR, Sonzogni L, Cavallini A, Foti L, Guerra V, Di Leo A, Mondelli MU, Misciagna G, Silini EM.; 1999 Jul; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=85170
- **Molecular Evidence of Male-to-Female Sexual Transmission of Hepatitis C Virus after Vaginal and Anal Intercourse.** by Halfon P, Riflet H, Renou C, Quentin Y, Cacoub P.; 2001 Mar; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=87908
- **Monitoring Response to Antiviral Therapy for Patients with Chronic Hepatitis C Virus Infection by a Core-Antigen Assay.** by Rebucci C, Cerino A, Cividini A, Timo L, Furione M, Mondelli MU.; 2003 Aug; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=179816
- **Multicenter Evaluation of the VERSANT HCV RNA Qualitative Assay for Detection of Hepatitis C Virus RNA.** by Hendricks DA, Friesenhahn M, Tanimoto L, Goergen B, Dodge D, Comanor L.; 2003 Feb; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=149721
- **Multicenter Quality Control for the Detection of Hepatitis C Virus RNA in Seminal Plasma Specimens.** by Bourlet T, Levy R, Laporte S, Blachier S, Bocket L, Cassuto G, Chollet L, Leruez-Ville M, Maertens A, Mousnier F, Pasquier C, Payan C, Pellegrin B, Schvoerer E, Zavadzki P, Chouteau J, Duverlie G, Izopet J, Lunel-Fabiani F, Pawlotsky JM, Profizi N, Rouzioux C, Stoll-Keller F, Thibault V, Wattre P, Pozzetto B.; 2003 Feb; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=149668
- **Multicycle infection of hepatitis C virus in cell culture and inhibition by alpha and beta interferons.** by Shimizu YK, Yoshikura H.; 1994 Dec; http://www.pubmedcentral.gov/picrender.fcgi?tool=pmcentrez&action=stream&blobtype=pdf&artid=237312
- **Multigene Tracking of Hepatitis C Virus Quasispecies after Liver Transplantation: Correlation of Genetic Diversification in the Envelope Region with Asymptomatic or Mild Disease Patterns.** by Sullivan DG, Wilson JJ, Carithers RL Jr, Perkins JD, Gretch DR.; 1998 Dec; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=110527
- **Mutational analysis of the hepatitis C virus RNA helicase.** by Kim DW, Kim J, Gwack Y, Han JH, Choe J.; 1997 Dec; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&rendertype=abstract&artid=230244

- **Mutations in Hepatitis C Virus RNAs Conferring Cell Culture Adaptation.** by Lohmann V, Korner F, Dobierzewska A, Bartenschlager R.; 2001 Feb 1; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=114050
- **Mutations that permit efficient replication of hepatitis C virus RNA in Huh-7 cells prevent productive replication in chimpanzees.** by Bukh J, Pietschmann T, Lohmann V, Krieger N, Faulk K, Engle RE, Govindarajan S, Shapiro M, St. Claire M, Bartenschlager R.; 2002 Oct 29; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=137898
- **Natural Variation in Translational Activities of the 5[prime prime or minute] Nontranslated RNAs of Hepatitis C Virus Genotypes 1a and 1b: Evidence for a Long-Range RNA-RNA Interaction outside of the Internal Ribosomal Entry Site.** by Honda M, Rijnbrand R, Abell G, Kim D, Lemon SM.; 1999 Jun; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=112538
- **Nested Restriction Site-Specific PCR To Detect and Type Hepatitis C Virus (HCV): a Rapid Method To Distinguish HCV Subtype 1b from Other Genotypes.** by Krekulova L, Rehak V, Wakil AE, Harris E, Riley LW.; 2001 May; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=88024
- **Neutralizing antibodies against hepatitis C virus and the emergence of neutralization escape mutant viruses.** by Shimizu YK, Hijikata M, Iwamoto A, Alter HJ, Purcell RH, Yoshikura H.; 1994 Mar; http://www.pubmedcentral.gov/picrender.fcgi?tool=pmcentrez&action=stream&blobtype=pdf&artid=236605
- **New hepatitis C virus (HCV) genotyping system that allows for identification of HCV genotypes 1a, 1b, 2a, 2b, 3a, 3b, 4, 5a, and 6a.** by Ohno O, Mizokami M, Wu RR, Saleh MG, Ohba K, Orito E, Mukaide M, Williams R, Lau JY.; 1997 Jan; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&rendertype=abstract&artid=229539
- **Nonenveloped Nucleocapsids of Hepatitis C Virus in the Serum of Infected Patients.** by Maillard P, Krawczynski K, Nitkiewicz J, Bronnert C, Sidorkiewicz M, Gounon P, Dubuisson J, Faure G, Crainic R, Budkowska A.; 2001 Sep 1; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=115068
- **Nonrandom Distribution of Hepatitis C Virus Quasispecies in Plasma and Peripheral Blood Mononuclear Cell Subsets.** by Afonso AM, Jiang J, Penin F, Tareau C, Samuel D, Petit MA, Bismuth H, Dussaix E, Feray C.; 1999 Nov; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=112955
- **Nonstructural protein 3 of hepatitis C virus blocks the distribution of the free catalytic subunit of cyclic AMP-dependent protein kinase.** by Borowski P, Oehlmann K, Heiland M, Laufs R.; 1997 Apr; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&rendertype=abstract&artid=191408
- **Nonstructural Protein 5A of Hepatitis C Virus Inhibits the Function of Karyopherin [beta]3.** by Chung KM, Lee J, Kim JE, Song OK, Cho S, Lim J, Seedorf M, Hahm B, Jang SK.; 2000 Jun 1; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=110877

- **Nonstructural Protein Precursor NS4A/B from Hepatitis C Virus Alters Function and Ultrastructure of Host Secretory Apparatus.** by Konan KV, Giddings, Jr. TH, Ikeda M, Li K, Lemon SM, Kirkegaard K.; 2003 Jul 15;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=161946
- **Novel Approach To Reduce the Hepatitis C Virus (HCV) Window Period: Clinical Evaluation of a New Enzyme-Linked Immunosorbent Assay for HCV Core Antigen.** by Icardi G, Ansaldi F, Bruzzone BM, Durando P, Lee S, de Luigi C, Crovari P.; 2001 Sep;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=88305
- **Nucleotide and Amino Acid Complexity of Hepatitis C Virus Quasispecies in Serum and Liver.** by Cabot B, Martell M, Esteban JI, Sauleda S, Otero T, Esteban R, Guardia J, Gomez J.; 2000 Jan 15;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=111600
- **Oligomerization and Cooperative RNA Synthesis Activity of Hepatitis C Virus RNA-Dependent RNA Polymerase.** by Wang QM, Hockman MA, Staschke K, Johnson RB, Case KA, Lu J, Parsons S, Zhang F, Rathnachalam R, Kirkegaard K, Colacino JM.; 2002 Apr 15;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=136118
- **Optimal Induction of Hepatitis C Virus Envelope-Specific Immunity by Bicistronic Plasmid DNA Inoculation with the Granulocyte-Macrophage Colony-Stimulating Factor Gene.** by Lee SW, Cho JH, Sung YC.; 1998 Oct;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=110238
- **Outbreak of Nosocomial Hepatitis C Virus Infection Resolved by Genetic Analysis of HCV RNA.** by Bruguera M, Saiz JC, Franco S, Gimenez-Barcons M, Sanchez-Tapias JM, Fabregas S, Vega R, Camps N, Dominguez A, Salleras L.; 2002 Nov;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=139636
- **Performance Characteristics of the COBAS Amplicor Hepatitis C Virus (HCV) Monitor, Version 2.0, International Unit Assay and the National Genetics Institute HCV Superquant Assay.** by Konnick EQ, Erali M, Ashwood ER, Hillyard DR.; 2002 Mar;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=120227
- **Performance of the COBAS AMPLICOR HCV MONITOR Test, Version 2.0, an Automated Reverse Transcription-PCR Quantitative System for Hepatitis C Virus Load Determination.** by Gerken G, Rothaar T, Rumi MG, Soffredini R, Trippler M, Blunk MJ, Butcher A, Soviero S, Colucci G.; 2000 Jun;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=86766
- **Performance of the New Bayer VERSANT HCV RNA 3.0 Assay for Quantitation of Hepatitis C Virus RNA in Plasma and Serum: Conversion to International Units and Comparison with the Roche COBAS Amplicor HCV Monitor, Version 2.0, Assay.** by Beld M, Sentjens R, Rebers S, Weegink C, Weel J, Sol C, Boom R.; 2002 Mar;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=120248
- **Persistent and Transient Replication of Full-Length Hepatitis C Virus Genomes in Cell Culture.** by Pietschmann T, Lohmann V, Kaul A, Krieger N, Rinck G, Rutter G, Strand D, Bartenschlager R.; 2002 Apr 15;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=136109

- **Persistent Hepatitis C Virus Infection in a Chimpanzee is Associated with Emergence of a Cytotoxic T Lymphocyte Escape Variant.** by Weiner A, Erickson AL, Kansopon J, Crawford K, Muchmore E, Hughes AL, Houghton M, Walker CM.; 1995 Mar 28; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&rendertype=abstract&artid=42297
- **Persistent Replication of Hepatitis C Virus Replicons Expressing the [beta]-Lactamase Reporter in Subpopulations of Highly Permissive Huh7 Cells.** by Murray EM, Grobler JA, Markel EJ, Pagnoni MF, Paonessa G, Simon AJ, Flores OA.; 2003 Mar 1; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=149762
- **Pharmacokinetics, Safety, and Antiviral Effects of Hypericin, a Derivative of St. John's Wort Plant, in Patients with Chronic Hepatitis C Virus Infection.** by Jacobson JM, Feinman L, Liebes L, Ostrow N, Koslowski V, Tobia A, Cabana BE, Lee DH, Spritzler J, Prince AM.; 2001 Feb; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=90321
- **Phosphorylation of the hepatitis C virus NS5A protein in vitro and in vivo: properties of the NS5A-associated kinase.** by Reed KE, Xu J, Rice CM.; 1997 Oct; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&rendertype=abstract&artid=192058
- **Phylogenetic Characterization of Genotype 4 Hepatitis C Virus Isolates from Argentina.** by Alfonso V, Flichman D, Sookoian S, Mbayed VA, Campos RH.; 2001 May; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=88066
- **Preclinical evaluation of AMPLICOR hepatitis C virus test for detection of hepatitis C virus RNA.** by Nolte FS, Thurmond C, Fried MW.; 1995 Jul; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&rendertype=abstract&artid=228267
- **Prevalence and significance of hepatitis C virus (HCV) viremia in HCV antibody-positive subjects from various populations.** by Francois M, Dubois F, Brand D, Bacq Y, Guerois C, Mouchet C, Tichet J, Goudeau A, Barin F.; 1993 May; http://www.pubmedcentral.gov/picrender.fcgi?tool=pmcentrez&action=stream&blobtype=pdf&artid=262901
- **Prevention of hepatitis C virus infection in chimpanzees after antibody-mediated in vitro neutralization.** by Farci P, Alter HJ, Wong DC, Miller RH, Govindarajan S, Engle R, Shapiro M, Purcell RH.; 1994 Aug 2; http://www.pubmedcentral.gov/picrender.fcgi?tool=pmcentrez&action=stream&blobtype=pdf&artid=44488
- **Prevention of hepatitis C virus infection in chimpanzees by hyperimmune serum against the hypervariable region 1 of the envelope 2 protein.** by Farci P, Shimoda A, Wong D, Cabezon T, De Gioannis D, Strazzera A, Shimizu Y, Shapiro M, Alter HJ, Purcell RH.; 1996 Dec 24; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=26415
- **Previously Infected and Recovered Chimpanzees Exhibit Rapid Responses That Control Hepatitis C Virus Replication upon Rechallenge.** by Major ME, Mihalik K, Puig M, Rehermann B, Nascimbeni M, Rice CM, Feinstone SM.; 2002 Jul 1; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=136282

- **Primary hepatocytes of Tupaia belangeri as a potential model for hepatitis C virus infection.** by Zhao X, Tang ZY, Klumpp B, Wolff-Vorbeck G, Barth H, Levy S, Weizsacker FV, Blum HE, Baumert TF.; 2002 Jan 15;
http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=150834
- **Production and Characterization of Monoclonal Antibodies Specific for a Conserved Epitope within Hepatitis C Virus Hypervariable Region 1.** by Li C, Candotti D, Allain JP.; 2001 Dec 15;
http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=116137
- **Prophylactic DNA vaccine for hepatitis C virus (HCV) infection: HCV-specific cytotoxic T lymphocyte induction and protection from HCV-recombinant vaccinia infection in an HLA-A2.1 transgenic mouse model.** by Arichi T, Saito T, Major ME, Belyakov IM, Shirai M, Engelhard VH, Feinstone SM, Berzofsky JA.; 2000 Jan 4;
http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=26657
- **Prospective Characterization of Full-Length Hepatitis C Virus NS5A Quasispecies during Induction and Combination Antiviral Therapy.** by Nousbaum JB, Polyak SJ, Ray SC, Sullivan DG, Larson AM, Carithers RL Jr, Gretch DR.; 2000 Oct 1;
http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=102099
- **Prospective Comparison of Whole-Blood- and Plasma-Based Hepatitis C Virus RNA Detection Systems: Improved Detection Using Whole Blood as the Source of Viral RNA.** by Stapleton JT, Klinzman D, Schmidt WN, Pfaller MA, Wu P, LaBrecque DR, Han JQ, Phillips MJ, Woolson R, Alden B.; 1999 Mar;
http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=84440
- **Prospective Multicenter Clinical Evaluation of AMPLICOR and COBAS AMPLICOR Hepatitis C Virus Tests.** by Nolte FS, Fried MW, Shiffman ML, Ferreira-Gonzalez A, Garrett CT, Schiff ER, Polyak SJ, Gretch DR.; 2001 Nov;
http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=88479
- **Protein Synthesis and Endoplasmic Reticulum Stress Can Be Modulated by the Hepatitis C Virus Envelope Protein E2 through the Eukaryotic Initiation Factor 2[alpha] Kinase PERK.** by Pavio N, Romano PR, Graczyk TM, Feinstone SM, Taylor DR.; 2003 Mar 15;
http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=149509
- **Protein-Protein Interactions between Hepatitis C Virus Nonstructural Proteins.** by Dimitrova M, Imbert I, Kieny MP, Schuster C.; 2003 May 1;
http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=153952
- **Qualitative Detection of Hepatitis C Virus RNA: Comparison of Analytical Sensitivity, Clinical Performance, and Workflow of the Cobas Amplicor HCV Test Version 2.0 and the HCV RNA Transcription-Mediated Amplification Qualitative Assay.** by Krajden M, Ziermann R, Khan A, Mak A, Leung K, Hendricks D, Comanor L.; 2002 Aug;
http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=120657
- **Quantification of Hepatitis C Virus (HCV) in Liver Specimens and Sera from Patients with Human Immunodeficiency Virus Coinfection by Using the Versant HCV RNA 3.0 (Branched DNA-Based) DNA Assay.** by Tedeschi R, Pivetta E, Zanussi S, Bidoli E, Ros M, di Gennaro G, Nasti G, De Paoli P.; 2003 Jul;
http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=165311

- **Quantification of Hepatitis C Virus in Human Liver and Serum Samples by Using LightCycler Reverse Transcriptase PCR.** by White PA, Pan Y, Freeman AJ, Marinos G, Ffrench RA, Lloyd AR, Rawlinson WD.; 2002 Nov; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=139708
- **Quantification of hepatitis C virus RNA by competitive amplification of RNA from denatured serum and hybridization on microtiter plates.** by Ravaggi A, Zonaro A, Mazza C, Albertini A, Cariani E.; 1995 Feb; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&rendertype=abstract&artid=227929
- **Quantitation of hepatitis C virus genome molecules in plasma samples.** by Manzin A, Bagnarelli P, Menzo S, Giostra F, Brugia M, Francesconi R, Bianchi FB, Clementi M.; 1994 Aug; http://www.pubmedcentral.gov/picrender.fcgi?tool=pmcentrez&action=stream&blobtype=pdf&artid=263907
- **Quantitative Assay of Hepatitis C Virus RNA Using an Automated Extraction System for Specific Capture with Probes and Paramagnetic Particle Separation.** by Miyachi H, Masukawa A, Asai S, Miura T, Tamatsukuri S, Hirose T, Ando Y.; 2003 Feb; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=149669
- **Quantitative Detection of Hepatitis C Virus RNA by Light Cycler PCR and Comparison with Two Different PCR Assays.** by Schroter M, Zollner B, Schafer P, Laufs R, Feucht HH.; 2001 Feb; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=87816
- **Reciprocal Interaction of Human Immunodeficiency Virus and Hepatitis C Virus Infections.** by Nelson KE, Thomas DL.; 2001 Sep; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=96162
- **Regulated processing of hepatitis C virus core protein is linked to subcellular localization.** by Liu Q, Tackney C, Bhat RA, Prince AM, Zhang P.; 1997 Jan; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&rendertype=abstract&artid=191098
- **Regulation of mRNA Translation and Cellular Signaling by Hepatitis C Virus Nonstructural Protein NS5A.** by He Y, Tan SL, Tareen SU, Vijaysri S, Langland JO, Jacobs BL, Katze MG.; 2001 Jun 1; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=114914
- **Regulation of PKR and IRF-1 during hepatitis C virus RNA replication.** by Pflugheber J, Fredericksen B, Sumpter R Jr, Wang C, Ware F, Sodora DL, Gale M Jr.; 2002 Apr 2; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=123702
- **Relevance of Reactivity in Commercially Available Hepatitis C Virus Antibody Assays.** by Polywka S, Schroter M, Feucht HH, Zollner B, Laufs R.; 2001 Apr; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=87996
- **Replication of Hepatitis C Virus Subgenomes in Nonhepatic Epithelial and Mouse Hepatoma Cells.** by Zhu Q, Guo JT, Seeger C.; 2003 Sep 1; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=187424
- **Replication Studies Using Genotype 1a Subgenomic Hepatitis C Virus Replicons.** by Gu B, Gates AT, Isken O, Behrens SE, Sarisky RT.; 2003 May 1; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=153987

- **Resistance Profile of a Hepatitis C Virus RNA-Dependent RNA Polymerase Benzothiadiazine Inhibitor.** by Nguyen TT, Gates AT, Gutshall LL, Johnston VK, Gu B, Duffy KJ, Sarisky RT.; 2003 Nov;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=253783
- **Restricted Isotypic Antibody Reactivity to Hepatitis C Virus Synthetic Peptides in Immunocompromised Patients.** by Devesa M, de Saez A, Leon G, Sirit F, Cosson C, Bermudez H, Liprandi F, Noya O, Pujol FH.; 1999 Mar;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=95702
- **Role of the 5[prime prime or minute]-Proximal Stem-Loop Structure of the 5[prime prime or minute] Untranslated Region in Replication and Translation of Hepatitis C Virus RNA.** by Luo G, Xin S, Cai Z.; 2003 Mar 1;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=149781
- **Role of the Asialoglycoprotein Receptor in Binding and Entry of Hepatitis C Virus Structural Proteins in Cultured Human Hepatocytes.** by Saunier B, Triyatni M, Ulianich L, Maruvada P, Yen P, Kohn LD.; 2003 Jan 1;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=140572
- **Screening for Hepatitis C Virus in Human Immunodeficiency Virus-Infected Individuals.** by Thio CL, Nolt KR, Astemborski J, Vlahov D, Nelson KE, Thomas DL.; 2000 Feb;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=86151
- **Search for Hepatitis C Virus Negative-Strand RNA Sequences and Analysis of Viral Sequences in the Central Nervous System: Evidence of Replication.** by Radkowski M, Wilkinson J, Nowicki M, Adair D, Vargas H, Ingui C, Rakela J, Laskus T.; 2002 Jan 15;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=136845
- **Secondary Structure of the 3[prime prime or minute] Terminus of Hepatitis C Virus Minus-Strand RNA.** by Schuster C, Isel C, Imbert I, Ehresmann C, Marquet R, Kieny MP.; 2002 Aug 15;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=155128
- **Selectable Subgenomic and Genome-Length Dicistronic RNAs Derived from an Infectious Molecular Clone of the HCV-N Strain of Hepatitis C Virus Replicate Efficiently in Cultured Huh7 Cells.** by Ikeda M, Yi M, Li K, Lemon SM.; 2002 Mar 1;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=135991
- **Selection of 3[prime prime or minute]-Template Bases and Initiating Nucleotides by Hepatitis C Virus NS5B RNA-Dependent RNA Polymerase.** by Shim JH, Larson G, Wu JZ, Hong Z.; 2002 Jul 15;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=136306
- **Selection of Functional Variants of the NS3-NS4A Protease of Hepatitis C Virus by Using Chimeric Sindbis Viruses.** by Filocamo G, Pacini L, Nardi C, Bartholomew L, Scaturro M, Delmastro P, Tramontano A, De Francesco R, Migliaccio G.; 1999 Jan;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=103862
- **Selection of RNA Aptamers That Are Specific and High-Affinity Ligands of the Hepatitis C Virus RNA-Dependent RNA Polymerase.** by Biroccio A, Hamm J, Incitti I, De Francesco R, Tomei L.; 2002 Apr 15;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=136087

- **Self-Assembly of Nucleocapsid-Like Particles from Recombinant Hepatitis C Virus Core Protein.** by Kunkel M, Lorinczi M, Rijnbrand R, Lemon SM, Watowich SJ.; 2001 Mar 1;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=114796
- **Sensitivity of the Procleix HIV-1/HCV Assay for Detection of Human Immunodeficiency Virus Type 1 and Hepatitis C Virus RNA in a High-Risk Population.** by Jackson JB, Smith K, Knott C, Korpela A, Simmons A, Piwowar-Manning E, McDonough S, Mimms L, Vargo JM.; 2002 Jul;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=120572
- **Sequence analysis of the 5' untranslated region in isolates of at least four genotypes of hepatitis C virus in The Netherlands.** by Kleter GE, van Doorn LJ, Brouwer JT, Schalm SW, Heijtink RA, Quint WG.; 1994 Feb;
  http://www.pubmedcentral.gov/picrender.fcgi?tool=pmcentrez&action=stream&blobtype=pdf&artid=263029
- **Sequence analysis of the core gene of 14 hepatitis C virus genotypes.** by Bukh J, Purcell RH, Miller RH.; 1994 Aug 16;
  http://www.pubmedcentral.gov/picrender.fcgi?tool=pmcentrez&action=stream&blobtype=pdf&artid=44581
- **Sequence evolution of the hypervariable region in the putative envelope region E2/NS1 of hepatitis C virus is correlated with specific humoral immune responses.** by van Doorn LJ, Capriles I, Maertens G, DeLeys R, Murray K, Kos T, Schellekens H, Quint W.; 1995 Feb;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&rendertype=abstract&artid=188641
- **Sequences in the 5[prime prime or minute] Nontranslated Region of Hepatitis C Virus Required for RNA Replication.** by Friebe P, Lohmann V, Krieger N, Bartenschlager R.; 2001 Dec 15;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=116100
- **Serological determination of hepatitis C virus genotype: comparison with a standardized genotyping assay.** by Pawlotsky JM, Prescott L, Simmonds P, Pellet C, Laurent-Puig P, Labonne C, Darthuy F, Remire J, Duval J, Buffet C, Etienne JP, Dhumeaux D, Dussaix E.; 1997 Jul;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&rendertype=abstract&artid=229831
- **Serological Determination of Hepatitis C Virus Subtypes 1a, 1b, 2a, 2b, 3a, and 4a by a Recombinant Immunoblot Assay.** by Schroter M, Feucht HH, Schafer P, Zollner B, Laufs R.; 1999 Aug;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=85286
- **Sialadenitis histologically resembling Sjogren syndrome in mice transgenic for hepatitis C virus envelope genes.** by Koike K, Moriya K, Ishibashi K, Yotsuyanagi H, Shintani Y, Fujie H, Kurokawa K, Matsuura Y, Miyamura T.; 1997 Jan 7;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=19297
- **Significance of highly positive c22-3 "indeterminate" second-generation hepatitis C virus (HCV) recombinant immunoblot assay (RIBA) and resolution by third-generation HCV RIBA.** by Pawlotsky JM, Fleury A, Choukroun V, Deforges L, Roudot-Thoraval F, Aumont P, Duval J, Dhumeaux D.; 1994 May;
  http://www.pubmedcentral.gov/picrender.fcgi?tool=pmcentrez&action=stream&blobtype=pdf&artid=263701

- **Significance of indeterminate third-generation hepatitis C virus recombinant immunoblot assay.** by Pawlotsky JM, Bastie A, Pellet C, Remire J, Darthuy F, Wolfe L, Sayada C, Duval J, Dhumeaux D.; 1996 Jan; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&rendertype=abstract&artid=228735
- **Significance of Pretreatment Analysis of Hepatitis C Virus Genotype 1b Hypervariable Region 1 Sequences To Predict Antiviral Outcome.** by Gaudy C, Moreau A, Veillon P, Temoin S, Lunel F, Goudeau A.; 2003 Aug; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=179854
- **Significant Closure of the Human Immunodeficiency Virus Type 1 and Hepatitis C Virus Preseroconversion Detection Windows with a Transcription-Mediated-Amplification-Driven Assay.** by Kolk DP, Dockter J, Linnen J, Ho-Sing-Loy M, Gillotte-Taylor K, McDonough SH, Mimms L, Giachetti C.; 2002 May; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=130666
- **Simple and Reliable Method for Detection and Genotyping of Hepatitis C Virus RNA in Dried Blood Spots Stored at Room Temperature.** by Solmone M, Girardi E, Costa F, Pucillo L, Ippolito G, Capobianchi MR.; 2002 Sep; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=130818
- **Simplified Hepatitis C Virus Genotyping by Heteroduplex Mobility Analysis.** by White PA, Zhai X, Carter I, Zhao Y, Rawlinson WD.; 2000 Feb; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=86128
- **Simultaneous Detection of Multiplex-Amplified Human Immunodeficiency Virus Type 1 RNA, Hepatitis C Virus RNA, and Hepatitis B Virus DNA Using a Flow Cytometer Microsphere-Based Hybridization Assay.** by Defoort JP, Martin M, Casano B, Prato S, Camilla C, Fert V.; 2000 Mar; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=86341
- **Specific Interaction between the Hepatitis C Virus NS5B RNA Polymerase and the 3[prime prime or minute] End of the Viral RNA.** by Cheng JC, Chang MF, Chang SC.; 1999 Aug; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=112794
- **Specific Interaction of Eukaryotic Translation Initiation Factor 3 with the 5[prime prime or minute] Nontranslated Regions of Hepatitis C Virus and Classical Swine Fever Virus RNAs.** by Sizova DV, Kolupaeva VG, Pestova TV, Shatsky IN, Hellen CU.; 1998 Jun; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=110013
- **Specific Interaction of Hepatitis C Virus Protease/Helicase NS3 with the 3[prime prime or minute]-Terminal Sequences of Viral Positive- and Negative-Strand RNA.** by Banerjee R, Dasgupta A.; 2001 Feb 15; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=114080
- **Stable hepatitis C virus RNA detection by RT-PCR during four days storage.** by de Moreau de Gerbehaye AI, Bodeus M, Robert A, Horsmans Y, Goubau P.; 2002; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=130053
- **Strengths and Limitations of Commercial Tests for Hepatitis C Virus RNA Quantification.** by Morishima C, Chung M, Ng KW, Brambilla DJ, Gretch DR.; 2004 Jan; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=321650

- **Structural Analysis of the Hepatitis C Virus RNA Polymerase in Complex with Ribonucleotides.** by Bressanelli S, Tomei L, Rey FA, De Francesco R.; 2002 Apr 1; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=136026
- **Structure and organization of the hepatitis C virus genome isolated from human carriers.** by Takamizawa A, Mori C, Fuke I, Manabe S, Murakami S, Fujita J, Onishi E, Andoh T, Yoshida I, Okayama H.; 1991 Mar; http://www.pubmedcentral.gov/picrender.fcgi?tool=pmcentrez&action=stream&blobtype=pdf&artid=239876
- **Structure of replicating hepatitis C virus (HCV) quasispecies in the liver may not be reflected by analysis of circulating HCV virions.** by Cabot B, Esteban JI, Martell M, Genesca J, Vargas V, Esteban R, Guardia J, Gomez J.; 1997 Feb; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&rendertype=abstract&artid=191240
- **Structure of the 3' terminus of the hepatitis C virus genome.** by Tanaka T, Kato N, Cho MJ, Sugiyama K, Shimotohno K.; 1996 May; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&rendertype=abstract&artid=190199
- **Structure-Based Mutagenesis Study of Hepatitis C Virus NS3 Helicase.** by Lin C, Kim JL.; 1999 Oct; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=112901
- **Structure-Based Mutational Analysis of the Hepatitis C Virus NS3 Helicase.** by Tai CL, Pan WC, Liaw SH, Yang UC, Hwang LH, Chen DS.; 2001 Sep 1; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=115073
- **Structure-Function Analysis of Hepatitis C Virus Envelope-CD81 Binding.** by Petracca R, Falugi F, Galli G, Norais N, Rosa D, Campagnoli S, Burgio V, Di Stasio E, Giardina B, Houghton M, Abrignani S, Grandi G.; 2000 May 15; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=112005
- **Study on reliability of commercially available hepatitis C virus antibody tests.** by Feucht HH, Zollner B, Polywka S, Laufs R.; 1995 Mar; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&rendertype=abstract&artid=228001
- **Subcellular Localization, Stability, and trans-Cleavage Competence of the Hepatitis C Virus NS3-NS4A Complex Expressed in Tetracycline-Regulated Cell Lines.** by Wolk B, Sansonno D, Krausslich HG, Dammacco F, Rice CM, Blum HE, Moradpour D.; 2000 Mar 1; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=111711
- **Subtype 2c of hepatitis C virus is highly prevalent in Italy and is heterogeneous in the NS5A region.** by Maggi F, Vatteroni ML, Fornai C, Morrica A, Giorgi M, Bendinelli M, Pistello M.; 1997 Jan; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&rendertype=abstract&artid=229530
- **Subtype analysis of hepatitis C virus in Indonesia on the basis of NS5b region sequences.** by Hotta H, Handajani R, Lusida MI, Soemarto W, Doi H, Miyajima H, Homma M.; 1994 Dec; http://www.pubmedcentral.gov/picrender.fcgi?tool=pmcentrez&action=stream&blobtype=pdf&artid=264225

- **Subversion of Cell Signaling Pathways by Hepatitis C Virus Nonstructural 5A Protein via Interaction with Grb2 and P85 Phosphatidylinositol 3-Kinase.** by He Y, Nakao H, Tan SL, Polyak SJ, Neddermann P, Vijaysri S, Jacobs BL, Katze MG.; 2002 Sep 15;
http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=136456
- **Survey of type 6 group variants of hepatitis C virus in Southeast Asia by using a core-based genotyping assay.** by Mellor J, Walsh EA, Prescott LE, Jarvis LM, Davidson F, Yap PL, Simmonds P.; 1996 Feb;
http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&rendertype=abstract&artid=228809
- **Tear fluid of hepatitis C virus carriers could be infectious.** by Feucht HH, Zollner B, Schroter M, Altrogge H, Laufs R.; 1995 Aug;
http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&rendertype=abstract&artid=228367
- **Template Requirements for De Novo RNA Synthesis by Hepatitis C Virus Nonstructural Protein 5B Polymerase on the Viral X RNA.** by Kim M, Kim H, Cho SP, Min MK.; 2002 Jul 15;
http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=136341
- **Template Requirements for RNA Synthesis by a Recombinant Hepatitis C Virus RNA-Dependent RNA Polymerase.** by Kao CC, Yang X, Kline A, Wang QM, Barket D, Heinz BA.; 2000 Dec 1;
http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=113194
- **Template/Primer Requirements and Single Nucleotide Incorporation by Hepatitis C Virus Nonstructural Protein 5B Polymerase.** by Zhong W, Ferrari E, Lesburg CA, Maag D, Ghosh SK, Cameron CE, Lau JY, Hong Z.; 2000 Oct 1;
http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=102112
- **The 3[prime prime or minute]-Untranslated Region of Hepatitis C Virus RNA Enhances Translation from an Internal Ribosomal Entry Site.** by Ito T, Tahara SM, Lai MM.; 1998 Nov;
http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=110295
- **The Arginine-1493 Residue in QRRGRTGR1493G Motif IV of the Hepatitis C Virus NS3 Helicase Domain Is Essential for NS3 Protein Methylation by the Protein Arginine Methyltransferase 1.** by Rho J, Choi S, Seong YR, Choi J, Im DS.; 2001 Sep 1;
http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=115047
- **The Clearance of Hepatitis C Virus Infection in Chimpanzees May Not Necessarily Correlate with the Appearance of Acquired Immunity.** by Thomson M, Nascimbeni M, Havert MB, Major M, Gonzales S, Alter H, Feinstone SM, Murthy KK, Rehermann B, Liang TJ.; 2003 Jan 15;
http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=140840
- **The helicase activity associated with hepatitis C virus nonstructural protein 3 (NS3).** by Tai CL, Chi WK, Chen DS, Hwang LH.; 1996 Dec;
http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&rendertype=abstract&artid=190938
- **The hepatitis C virus internal ribosome entry site facilitates efficient protein synthesis in blood vessel endothelium during tumour angiogenesis.** by Chung GT, Yamada Y, Pannell R, Forster A, Rabbitts TH.; 2003 Apr 15;
http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=153758

- **The hepatitis C virus NS4A protein: interactions with the NS4B and NS5A proteins.** by Lin C, Wu JW, Hsiao K, Su MS.; 1997 Sep; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&rendertype=abstract&artid=191920
- **The hepatitis C virus p7 protein forms an ion channel that is inhibited by long-alkyl-chain iminosugar derivatives.** by Pavlovic D, Neville DC, Argaud O, Blumberg B, Dwek RA, Fischer WB, Zitzmann N.; 2003 May 13; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=156333
- **The La antigen binds 5[prime prime or minute] noncoding region of the hepatitis C virus RNA in the context of the initiator AUG codon and stimulates internal ribosome entry site-mediated translation.** by Ali N, Siddiqui A.; 1997 Mar 18; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=20073
- **The Native Form and Maturation Process of Hepatitis C Virus Core Protein.** by Yasui K, Wakita T, Tsukiyama-Kohara K, Funahashi SI, Ichikawa M, Kajita T, Moradpour D, Wands JR, Kohara M.; 1998 Jul; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=110410
- **The NS2 protein of hepatitis C virus is a transmembrane polypeptide.** by Santolini E, Pacini L, Fipaldini C, Migliaccio G, Monica N.; 1995 Dec; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&rendertype=abstract&artid=189684
- **The p7 polypeptide of hepatitis C virus is critical for infectivity and contains functionally important genotype-specific sequences.** by Sakai A, Claire MS, Faulk K, Govindarajan S, Emerson SU, Purcell RH, Bukh J.; 2003 Sep 30; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=208812
- **The Ribosome Binding Site of Hepatitis C Virus mRNA.** by Lytle JR, Wu L, Robertson HD.; 2001 Aug 15; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=114998
- **Three Cases of Infection with Hepatitis C Virus Genotype 5 among Brazilian Hepatitis Patients.** by Levi JE, Takaoka DT, Garrini RH, Fachini RM, Focaccia R, de Bortholi Santos E, Mitre HP, de Mendonca JS, de Paula Cavalheiro N, Barone AA, Wendel S.; 2002 Jul; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=120608
- **Tracking hepatitis C virus quasispecies major and minor variants in symptomatic and asymptomatic liver transplant recipients.** by Gretch DR, Polyak SJ, Wilson JJ, Carithers RL Jr, Perkins JD, Corey L.; 1996 Nov; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&rendertype=abstract&artid=190831
- **Transcriptional Activation of the Interleukin-2 Promoter by Hepatitis C Virus Core Protein.** by Bergqvist A, Rice CM.; 2001 Jan 15; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=113973
- **Transcripts from a single full-length cDNA clone of hepatitis C virus are infectious when directly transfected into the liver of a chimpanzee.** by Yanagi M, Purcell RH, Emerson SU, Bukh J.; 1997 Aug 5; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=23104
- **Transfection of a differentiated human hepatoma cell line (Huh7) with in vitro-transcribed hepatitis C virus (HCV) RNA and establishment of a long-term culture**

persistently infected with HCV. by Yoo BJ, Selby MJ, Choe J, Suh BS, Choi SH, Joh JS, Nuovo GJ, Lee HS, Houghton M, Han JH.; 1995 Jan;
http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&rendertype=abstract&artid=188545

- **Transient immunoglobulin M antibody response to hepatitis C virus capsid antigen in posttransfusion hepatitis C: putative serological marker for acute viral infection.** by Chen PJ, Wang JT, Hwang LH, Yang YH, Hsieh CL, Kao JH, Sheu JC, Lai MY, Wang TH, Chen DS.; 1992 Jul 1;
http://www.pubmedcentral.gov/picrender.fcgi?tool=pmcentrez&action=stream&blobtype=pdf&artid=402120
- **Translation of human hepatitis C virus RNA in cultured cells is mediated by an internal ribosome-binding mechanism.** by Wang C, Sarnow P, Siddiqui A.; 1993 Jun;
http://www.pubmedcentral.gov/picrender.fcgi?tool=pmcentrez&action=stream&blobtype=pdf&artid=237677
- **Transmission of Hepatitis C Virus in a Gynecological Surgery Setting.** by Massari M, Petrosillo N, Ippolito G, Solforosi L, Bonazzi L, Clementi M, Manzin A.; 2001 Aug;
http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=88251
- **Triple Decoding of Hepatitis C Virus RNA by Programmed Translational Frameshifting.** by Choi J, Xu Z, Ou JH.; 2003 Mar 1;
http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=151691
- **Two Successive Hepatitis C Virus Infections in an Intravenous Drug User.** by Proust B, Dubois F, Bacq Y, Le Pogam S, Rogez S, Levillain R, Goudeau A.; 2000 Aug;
http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=87209
- **Uneven Distribution of Hepatitis C Virus Quasispecies in Tissues from Subjects with End-Stage Liver Disease: Confounding Effect of Viral Adsorption and Mounting Evidence for the Presence of Low-Level Extrahepatic Replication.** by Laskus T, Radkowski M, Wang LF, Nowicki M, Rakela J.; 2000 Jan 15;
http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=111624
- **Upregulation of Major Histocompatibility Complex Class I on Liver Cells by Hepatitis C Virus Core Protein via p53 and TAP1 Impairs Natural Killer Cell Cytotoxicity.** by Herzer K, Falk CS, Encke J, Eichhorst ST, Ulsenheimer A, Seliger B, Krammer PH.; 2003 Aug 1;
http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=165225
- **Use of a signature nucleotide sequence of hepatitis C virus for detection of viral RNA in human serum and plasma.** by Cha TA, Kolberg J, Irvine B, Stempien M, Beall E, Yano M, Choo QL, Houghton M, Kuo G, Han JH, et al.; 1991 Nov;
http://www.pubmedcentral.gov/picrender.fcgi?tool=pmcentrez&action=stream&blobtype=pdf&artid=270367
- **Use of aminotransferase, hepatitis C antibody, and hepatitis C polymerase chain reaction RNA assays to establish the diagnosis of hepatitis C virus infection in a diagnostic virology laboratory.** by Gretch D, Lee W, Corey L.; 1992 Aug;
http://www.pubmedcentral.gov/picrender.fcgi?tool=pmcentrez&action=stream&blobtype=pdf&artid=265459
- **Use of Phylogenetic Analysis of Hepatitis C Virus (HCV) Hypervariable Region 1 Sequences To Trace an Outbreak of HCV in an Autodialysis Unit.** by Halfon P, Roubicek C, Gerolami V, Quentin Y, Khiri H, Pepe G, Berland Y.; 2002 Apr;
http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=140339

- **Use of Whole Blood Specimens for Routine Clinical Quantitation of Hepatitis C Virus RNA Does Not Increase Assay Sensitivity.** by Cook L, Ross AM, Knight GB, Agnello V.; 2000 Dec;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=87600
- **Viral and Cellular Determinants of Hepatitis C Virus RNA Replication in Cell Culture.** by Lohmann V, Hoffmann S, Herian U, Penin F, Bartenschlager R.; 2003 Mar 1;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=149776
- **Viral and immunological determinants of hepatitis C virus clearance, persistence, and disease.** by Thimme R, Bukh J, Spangenberg HC, Wieland S, Pemberton J, Steiger C, Govindarajan S, Purcell RH, Chisari FV.; 2002 Nov 26;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=137773
- **Viral RNA Mutations Are Region Specific and Increased by Ribavirin in a Full-Length Hepatitis C Virus Replication System.** by Contreras AM, Hiasa Y, He W, Terella A, Schmidt EV, Chung RT.; 2002 Sep 1;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=136407
- **Virological features of hepatitis C virus infection in hemodialysis patients.** by Silini E, Bono F, Cerino A, Piazza V, Solcia E, Mondelli MU.; 1993 Nov;
  http://www.pubmedcentral.gov/picrender.fcgi?tool=pmcentrez&action=stream&blobtype=pdf&artid=266154
- **Virus-Host Cell Interactions during Hepatitis C Virus RNA Replication: Impact of Polyprotein Expression on the Cellular Transcriptome and Cell Cycle Association with Viral RNA Synthesis.** by Scholle F, Li K, Bodola F, Ikeda M, Luxon BA, Lemon SM.; 2004 Feb 1;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=321413
- **Whole-Blood Hepatitis C Virus RNA Extraction Methods.** by Schmidt W.; 2001 Oct;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=88445
- **Yellow Fever Virus Replicons as an Expression System for Hepatitis C Virus Structural Proteins.** by Molenkamp R, Kooi EA, Lucassen MA, Greve S, Thijssen JC, Spaan WJ, Bredenbeek PJ.; 2003 Jan 15;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=140782

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To generate your own bibliography of studies dealing with hepatitis C virus, simply go to the PubMed Web site at **http://www.ncbi.nlm.nih.gov/pubmed**. Type "hepatitis C virus" (or synonyms) into the search box, and click "Go." The following is the type of output you can expect from PubMed for hepatitis C virus (hyperlinks lead to article summaries):

- **A 48-week duration of therapy with pegylated interferon alpha 2b plus ribavirin may be too short to maximize long-term response among patients infected with genotype-1 hepatitis C virus.**
  Author(s): Drusano GL, Preston SL.
  Source: The Journal of Infectious Diseases. 2004 March 15; 189(6): 964-70. Epub 2004 February 27.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14999598

- **A cis-acting replication element in the sequence encoding the NS5B RNA-dependent RNA polymerase is required for hepatitis C virus RNA replication.**
  Author(s): You S, Stump DD, Branch AD, Rice CM.
  Source: Journal of Virology. 2004 February; 78(3): 1352-66.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14722290

- **A conserved basic loop in hepatitis C virus p7 protein is required for amantadine-sensitive ion channel activity in mammalian cells but is dispensable for localization to mitochondria.**
  Author(s): Griffin SD, Harvey R, Clarke DS, Barclay WS, Harris M, Rowlands DJ.
  Source: The Journal of General Virology. 2004 February; 85(Pt 2): 451-61.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14769903

- **A health economic model to assess the long term effects and cost-effectiveness of PEG IFN alpha-2a in hepatitis C virus infected patients.**
  Author(s): Annemans L, Warie H, Nechelput M, Peraux B.
  Source: Acta Gastroenterol Belg. 2004 January-March; 67(1): 1-8.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15149079

- **A novel antigen detection immunoassay for field diagnosis of hepatitis C virus infection.**
  Author(s): Attallah AM, Ismail H, Tabll AA, Shiha GE, El-Dosoky I.
  Source: Journal of Immunoassay & Immunochemistry. 2003; 24(4): 395-407.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14677657

- **A peptide from autoantigen La blocks poliovirus and hepatitis C virus cap-independent translation and reveals a single tyrosine critical for La RNA binding and translation stimulation.**
  Author(s): Izumi RE, Das S, Barat B, Raychaudhuri S, Dasgupta A.
  Source: Journal of Virology. 2004 April; 78(7): 3763-76.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15016896

- **A rational use of laboratory tests in the diagnosis and management of hepatitis C virus infection.**
  Author(s): Dal Molin G, Tiribelli C, Campello C.
  Source: Ann Hepatol. 2003 April-June; 2(2): 76-83. Review.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15041895

- **Absence of antibodies to cyclic citrullinated peptide in sera of patients with hepatitis C virus infection and cryoglobulinemia.**
  Author(s): Wener MH, Hutchinson K, Morishima C, Gretch DR.
  Source: Arthritis and Rheumatism. 2004 July; 50(7): 2305-8.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15248231

- **Absence of hepatitis C virus infection among patients with lymphoproliferative disorders in northern India.**
  Author(s): Varma S, Dhiman RK, Srivastava D, Malhotra P, Chawla Y.
  Source: Gastroenterology. 2004 May; 126(5): 1498-9; Author Reply 1499.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15131829

- **Accelerated decline in lung function and impaired reversibility with salbutamol in asthmatic patients with chronic hepatitis C virus infection: a 6-year follow-up study.**
  Author(s): Kanazawa H, Yoshikawa J.
  Source: The American Journal of Medicine. 2004 June 1; 116(11): 749-52.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15144911

- **Activation of the CKI-CDK-Rb-E2F pathway in full genome hepatitis C virus-expressing cells.**
  Author(s): Tsukiyama-Kohara K, Tone S, Maruyama I, Inoue K, Katsume A, Nuriya H, Ohmori H, Ohkawa J, Taira K, Hoshikawa Y, Shibasaki F, Reth M, Minatogawa Y, Kohara M.
  Source: The Journal of Biological Chemistry. 2004 April 9; 279(15): 14531-41. Epub 2004 January 26.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14747471

- **Acute hepatitis C virus infection, 1986-2001: a rare cause of fulminant hepatitis in Chiba, Japan.**
  Author(s): Kanda T, Yokosuka O, Imazeki F, Saisho H.
  Source: Hepatogastroenterology. 2004 March-April; 51(56): 556-8.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15086201

- **Acute hepatitis C virus infection: to treat or not to treat?**
  Author(s): Jaeckel E, Wedemeyer H, Wiegand J, Manns MP.
  Source: Gastroenterology. 2004 April; 126(4): 1219-20; Author Reply 1220.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15057772

- **Adaptive mutations producing efficient replication of genotype 1a hepatitis C virus RNA in normal Huh7 cells.**
  Author(s): Yi M, Lemon SM.
  Source: Journal of Virology. 2004 August; 78(15): 7904-15.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15254163

- **Alternative approaches for efficient inhibition of hepatitis C virus RNA replication by small interfering RNAs.**
  Author(s): Kronke J, Kittler R, Buchholz F, Windisch MP, Pietschmann T, Bartenschlager R, Frese M.
  Source: Journal of Virology. 2004 April; 78(7): 3436-46.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15016866

- **Amantadine therapy in renal transplant patients with hepatitis C virus infection.**
  Author(s): Kamar N, Rostaing L, Sandres-Saune K, Ribes D, Durand D, Izopet J.
  Source: Journal of Clinical Virology : the Official Publication of the Pan American Society for Clinical Virology. 2004 May; 30(1): 110-4.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15072764

- **An outbreak of hepatitis C virus in a haemodialysis unit: molecular evidence of patient-to-patient transmission.**
  Author(s): Ansaldi F, Bruzzone B, de Florentiis D, Marasso P, Gota F, Mofferdin A, Campello C, Crovari P, Icardi G.
  Source: Ann Ig. 2003 September-October; 15(5): 685-91.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14969322

- **Analysis of B-lymphocyte differentiation in patients infected with hepatitis C virus.**
  Author(s): Fournillier A, Freida D, Defrance T, Merle P, Trepo C, Inchauspe G.
  Source: Journal of Medical Virology. 2004 April; 72(4): 566-74.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14981759

- **Antiapoptotic regulation by hepatitis C virus core protein through up-regulation of inhibitor of caspase-activated DNase.**
  Author(s): Sacco R, Tsutsumi T, Suzuki R, Otsuka M, Aizaki H, Sakamoto S, Matsuda M, Seki N, Matsuura Y, Miyamura T, Suzuki T.
  Source: Virology. 2003 December 5; 317(1): 24-35.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14675622

- **Aspects of immune nonspecific and CD19+ cell changes in alcoholic liver disease with or without chronic hepatitis C virus infection.**
  Author(s): Mos L, Plesa A.
  Source: Rom J Gastroenterol. 2003 December; 12(4): 267-72.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14726969

- **Bacterial cell surface display for epitope mapping of hepatitis C virus core antigen.**
  Author(s): Kang SM, Rhee JK, Kim EJ, Han KH, Oh JW.
  Source: Fems Microbiology Letters. 2003 September 26; 226(2): 347-53.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14553932

- **B-cell lymphomas involving the skin associated with hepatitis C virus infection.**
  Author(s): Viguier M, Rivet J, Agbalika F, Kerviler E, Brice P, Dubertret L, Bachelez H.
  Source: International Journal of Dermatology. 2002 September; 41(9): 577-82.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12358827

- **B-cell non-Hodgkin's lymphoma and hepatitis C virus infection: a systematic review.**
  Author(s): Negri E, Little D, Boiocchi M, La Vecchia C, Franceschi S.
  Source: International Journal of Cancer. Journal International Du Cancer. 2004 August 10; 111(1): 1-8. Review.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15185336

- **BHIVA guidelines: coinfection with HIV and chronic hepatitis C virus.**
  Author(s): Nelson MR, Matthews G, Brook MG, Main J; British HIV Association.
  Source: Hiv Medicine. 2003 October; 4 Suppl 1: 52-62.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14511248

- **Biclonal multiple myeloma in liver cirrhosis due to hepatitis C virus infection.**
  Author(s): Tashiro M, Tabaru A, Narita R, Sugihara Y, Otsuki M.
  Source: Journal of Gastroenterology. 2003; 38(10): 1017-8.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14614615

- **Binding of the hepatitis C virus E2 glycoprotein to CD81 is strain specific and is modulated by a complex interplay between hypervariable regions 1 and 2.**
  Author(s): Roccasecca R, Ansuini H, Vitelli A, Meola A, Scarselli E, Acali S, Pezzanera M, Ercole BB, McKeating J, Yagnik A, Lahm A, Tramontano A, Cortese R, Nicosia A.
  Source: Journal of Virology. 2003 February; 77(3): 1856-67.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12525620

- **Biochemical markers of liver fibrosis in patients infected by hepatitis C virus: longitudinal validation in a randomized trial.**
  Author(s): Poynard T, Imbert-Bismut F, Ratziu V, Chevret S, Jardel C, Moussalli J, Messous D, Degos F; GERMED cyt04 group.
  Source: Journal of Viral Hepatitis. 2002 March; 9(2): 128-33.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=11876795

- **Biological and clinical significance of endotoxemia in the course of hepatitis C virus infection.**
  Author(s): Caradonna L, Mastronardi ML, Magrone T, Cozzolongo R, Cuppone R, Manghisi OG, Caccavo D, Pellegrino NM, Amoroso A, Jirillo E, Amati L.
  Source: Current Pharmaceutical Design. 2002; 8(11): 995-1005. Review.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=11945146

- **Biophysical characterization of hepatitis C virus core protein: implications for interactions within the virus and host.**
  Author(s): Kunkel M, Watowich SJ.
  Source: Febs Letters. 2004 January 16; 557(1-3): 174-80.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14741363

- **Blood exposures and hepatitis C virus infections among emergency responders.**
  Author(s): Datta SD, Armstrong GL, Roome AJ, Alter MJ.
  Source: Archives of Internal Medicine. 2003 November 24; 163(21): 2605-10.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14638560

- **Broad specificity of virus-specific CD4+ T-helper-cell responses in resolved hepatitis C virus infection.**
  Author(s): Day CL, Lauer GM, Robbins GK, McGovern B, Wurcel AG, Gandhi RT, Chung RT, Walker BD.
  Source: Journal of Virology. 2002 December; 76(24): 12584-95.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12438584

- **Broadly cross-reactive mimotope of hypervariable region 1 of hepatitis C virus derived from DNA shuffling and screened by phage display library.**
  Author(s): Zhang XX, Deng Q, Zhang SY, Liu J, Cai Q, Lu ZM, Wang Y.
  Source: Journal of Medical Virology. 2003 December; 71(4): 511-7.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14556263

- **CC chemokine receptor 5 delta32 polymorphism in two independent cohorts of hepatitis C virus infected patients without hemophilia.**
  Author(s): Wasmuth HE, Werth A, Mueller T, Berg T, Dietrich CG, Geier A, Schirin-Sokhan R, Gartung C, Lorenzen J, Matern S, Lammert F.
  Source: Journal of Molecular Medicine (Berlin, Germany). 2004 January; 82(1): 64-9. Epub 2003 December 13.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14673528

- **CD81 is an entry coreceptor for hepatitis C virus.**
  Author(s): Cormier EG, Tsamis F, Kajumo F, Durso RJ, Gardner JP, Dragic T.
  Source: Proceedings of the National Academy of Sciences of the United States of America. 2004 May 11; 101(19): 7270-4. Epub 2004 May 03.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15123813

- **Cell cycle perturbation in a human hepatoblastoma cell line constitutively expressing Hepatitis C virus core protein.**
  Author(s): Ruggieri A, Murdolo M, Harada T, Miyamura T, Rapicetta M.
  Source: Archives of Virology. 2004 January; 149(1): 61-74. Epub 2003 September 22.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14689276

- **Cellular RNA helicase p68 relocalization and interaction with the hepatitis C virus (HCV) NS5B protein and the potential role of p68 in HCV RNA replication.**
  Author(s): Goh PY, Tan YJ, Lim SP, Tan YH, Lim SG, Fuller-Pace F, Hong W.
  Source: Journal of Virology. 2004 May; 78(10): 5288-98.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15113910

- **Challenges in the management of HIV and hepatitis C virus co-infection.**
  Author(s): Lee W, Dieterich D.
  Source: Drugs. 2004; 64(7): 693-700. Review.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15025544

- **Changes in haemoglobin during interferon alpha-2b plus ribavirin combination therapy for chronic hepatitis C virus infection.**
  Author(s): Sulkowski MS, Wasserman R, Brooks L, Ball L, Gish R.
  Source: Journal of Viral Hepatitis. 2004 May; 11(3): 243-50.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15117326

- **Characterization of functional hepatitis C virus envelope glycoproteins.**
  Author(s): Op De Beeck A, Voisset C, Bartosch B, Ciczora Y, Cocquerel L, Keck Z, Foung S, Cosset FL, Dubuisson J.
  Source: Journal of Virology. 2004 March; 78(6): 2994-3002.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14990718

- **Characterization of infectious retroviral pseudotype particles bearing hepatitis C virus glycoproteins.**
  Author(s): Flint M, Logvinoff C, Rice CM, McKeating JA.
  Source: Journal of Virology. 2004 July; 78(13): 6875-82.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15194763

- **Characterization of the genome and structural proteins of hepatitis C virus resolved from infected human liver.**
  Author(s): Nielsen SU, Bassendine MF, Burt AD, Bevitt DJ, Toms GL.
  Source: The Journal of General Virology. 2004 June; 85(Pt 6): 1497-507.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15166434

- **Characterization of the hepatitis C virus RNA replication complex associated with lipid rafts.**
  Author(s): Aizaki H, Lee KJ, Sung VM, Ishiko H, Lai MM.
  Source: Virology. 2004 July 1; 324(2): 450-61.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15207630

- **Characterization of the inhibition of hepatitis C virus RNA replication by nonnucleosides.**
  Author(s): Tomei L, Altamura S, Bartholomew L, Bisbocci M, Bailey C, Bosserman M, Cellucci A, Forte E, Incitti I, Orsatti L, Koch U, De Francesco R, Olsen DB, Carroll SS, Migliaccio G.
  Source: Journal of Virology. 2004 January; 78(2): 938-46.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14694125

- **Cholestatic hepatitis due to hepatitis C virus after a living donor liver transplantation.**
  Author(s): Kaneko J, Sugawara Y, Akamatsu N, Kokudo N, Makuuchi M.
  Source: Hepatogastroenterology. 2004 January-February; 51(55): 243-4.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15011874

- **Clinical features related to antiphospholipid syndrome in patients with chronic viral infections (hepatitis C virus/HIV infection): description of 82 cases.**
  Author(s): Ramos-Casals M, Cervera R, Lagrutta M, Medina F, Garcia-Carrasco M, de la Red G, Bove A, Ingelmo M, Font J; Hispanoamerican Study Group of Autoimmune Manifestations of Chronic Viral Disease (HISPAMEC).
  Source: Clinical Infectious Diseases : an Official Publication of the Infectious Diseases Society of America. 2004 April 1; 38(7): 1009-16. Epub 2004 March 15.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15034835

- **Cloning and identification of NS5ATP2 gene and its spliced variant transactivated by hepatitis C virus non-structural protein 5A.**
  Author(s): Yang Q, Cheng J, Liu Y, Hong Y, Wang JJ, Zhang SL.
  Source: World Journal of Gastroenterology : Wjg. 2004 June 15; 10(12): 1735-9.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15188496

- **Co-infection with hepatitis C virus and human immunodeficiency virus among patients with sexually transmitted diseases in Pondicherry, South India.**
  Author(s): Bhattacharya S, Badrinath S, Hamide A, Sujatha S.
  Source: Indian J Pathol Microbiol. 2003 July; 46(3): 495-7.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15025322

- **Comparison of IFN-alpha 2b with or without ribavirin for treatment of chronic hepatitis C in HIV-positive patients infected with hepatitis C virus genotype 3a.**
  Author(s): Morsica G, Bruno R, Bagaglio S, De Mitri MS, Andreone P, Lazzarin A.
  Source: Aids (London, England). 2004 April 30; 18(7): 1080-2.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15096817

- **Conserved C-terminal threonine of hepatitis C virus NS3 regulates autoproteolysis and prevents product inhibition.**
  Author(s): Wang W, Lahser FC, Yi M, Wright-Minogue J, Xia E, Weber PC, Lemon SM, Malcolm BA.
  Source: Journal of Virology. 2004 January; 78(2): 700-9.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14694101

- **Conserved hierarchy of helper T cell responses in a chimpanzee during primary and secondary hepatitis C virus infections.**
  Author(s): Shoukry NH, Sidney J, Sette A, Walker CM.
  Source: Journal of Immunology (Baltimore, Md. : 1950). 2004 January 1; 172(1): 483-92.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14688358

- **Control of heterologous hepatitis C virus infection in chimpanzees is associated with the quality of vaccine-induced peripheral T-helper immune response.**
  Author(s): Rollier C, Depla E, Drexhage JA, Verschoor EJ, Verstrepen BE, Fatmi A, Brinster C, Fournillier A, Whelan JA, Whelan M, Jacobs D, Maertens G, Inchauspe G, Heeney JL.
  Source: Journal of Virology. 2004 January; 78(1): 187-96.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14671100

- **Cucumber mosaic virus as carrier of a hepatitis C virus-derived epitope.**
  Author(s): Natilla A, Piazzolla G, Nuzzaci M, Saldarelli P, Tortorella C, Antonaci S, Piazzolla P.
  Source: Archives of Virology. 2004 January; 149(1): 137-54. Epub 2003 September 22.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14689280

- **Decrease in the hepatitis C virus (HCV) prevalence in hemodialysis patients in Spain: effect of time, initiating HCV prevalence studies and adoption of isolation measures.**
  Author(s): Barril G, Traver JA.
  Source: Antiviral Research. 2003 October; 60(2): 129-34.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14638409

- **Detection of hepatitis C virus RNA in paraffin-embedded tissues from patients with non-Hodgkin's lymphoma.**
  Author(s): Paydas S, Ergin M, Tanriverdi K, Yavuz S, Disel U, Kilic NB, Erdogan S, Sahin B, Tuncer I, Burgut R.
  Source: American Journal of Hematology. 2004 July; 76(3): 252-7.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15224361

- **Development and evaluation of a quantitative competitive reverse transcription polymerase chain reaction (RT-PCR) for hepatitis C virus RNA in serum using transcribed thio-RNA as internal control.**
  Author(s): Hazari S, Acharya SK, Panda SK.
  Source: Journal of Virological Methods. 2004 March 1; 116(1): 45-54.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14715306

- **Development of a GB virus B marmoset model and its validation with a novel series of hepatitis C virus NS3 protease inhibitors.**
  Author(s): Bright H, Carroll AR, Watts PA, Fenton RJ.
  Source: Journal of Virology. 2004 February; 78(4): 2062-71.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14747571

- **Different hepatitis C virus dynamics of free-virions and immune-complexes after initiation of interferon-alpha in patients with chronic hepatitis C.**
  Author(s): Fujita N, Kaito M, Takeo M, Horiike S, Tanaka H, Ikoma J, Watanabe S, Adachi Y.
  Source: Journal of Hepatology. 2003 December; 39(6): 1013-9.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14642620

- **Differential activation of interferon-inducible genes by hepatitis C virus core protein mediated by the interferon stimulated response element.**
  Author(s): Dansako H, Naganuma A, Nakamura T, Ikeda F, Nozaki A, Kato N.
  Source: Virus Research. 2003 November; 97(1): 17-30.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14550584

- **Direct binding of hepatitis C virus core to gC1qR on CD4+ and CD8+ T cells leads to impaired activation of Lck and Akt.**
  Author(s): Yao ZQ, Eisen-Vandervelde A, Waggoner SN, Cale EM, Hahn YS.
  Source: Journal of Virology. 2004 June; 78(12): 6409-19.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15163734

- **Direct comparison of hepatitis C virus genotypes tested by INNO-LiPA HCV II and TRUGENE HCV genotyping methods.**
  Author(s): Zheng X, Pang M, Chan A, Roberto A, Warner D, Yen-Lieberman B.
  Source: Journal of Clinical Virology : the Official Publication of the Pan American Society for Clinical Virology. 2003 October; 28(2): 214-6.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12957191

- **Direct interaction between alpha-actinin and hepatitis C virus NS5B.**
  Author(s): Lan S, Wang H, Jiang H, Mao H, Liu X, Zhang X, Hu Y, Xiang L, Yuan Z.
  Source: Febs Letters. 2003 November 20; 554(3): 289-94.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14623081

- **Disappearance of gastric mucosa-associated lymphoid tissue in hepatitis C virus-positive patients after anti-hepatitis C virus therapy.**
  Author(s): Tursi A, Brandimarte G, Torello M.
  Source: Journal of Clinical Gastroenterology. 2004 April; 38(4): 360-3.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15087696

- **Discussion on spontaneous resolution of chronic hepatitis C virus after withdrawal of immunosuppression.**
  Author(s): Neumann UP, Neuhaus P.
  Source: Gastroenterology. 2004 February; 126(2): 627; Author Reply 627-8.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14765397

- **Disruption of hepatitis C virus RNA replication through inhibition of host protein geranylgeranylation.**
  Author(s): Ye J, Wang C, Sumpter R Jr, Brown MS, Goldstein JL, Gale M Jr.
  Source: Proceedings of the National Academy of Sciences of the United States of America. 2003 December 23; 100(26): 15865-70. Epub 2003 Dec 10.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14668447

- **Distribution of hepatitis C virus genotypes in patients with chronic hepatitis C infection in India.**
  Author(s): Singh S, Malhotra V, Sarin SK.
  Source: The Indian Journal of Medical Research. 2004 April; 119(4): 145-8.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15147119

- **Does bleach disinfection of syringes help prevent hepatitis C virus transmission?**
  Author(s): Hagan H, Thiede H.
  Source: Epidemiology (Cambridge, Mass.). 2003 September; 14(5): 628-9; Author Reply 629.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14501280

- **Does hepatitis C virus infection increase hematocrit and hemoglobin levels in hemodialyzed patients?**
  Author(s): Sahin I, Arabaci F, Sahin HA, Ilhan M, Ustun Y, Mercan R, Eminov L.
  Source: Clinical Nephrology. 2003 December; 60(6): 401-4.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14690257

- **Dominant negative effect of wild-type NS5A on NS5A-adapted subgenomic hepatitis C virus RNA replicon.**
  Author(s): Graziani R, Paonessa G.
  Source: The Journal of General Virology. 2004 July; 85(Pt 7): 1867-75.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15218171

- **Down-regulation of viral replication by adenoviral-mediated expression of siRNA against cellular cofactors for hepatitis C virus.**
  Author(s): Zhang J, Yamada O, Sakamoto T, Yoshida H, Iwai T, Matsushita Y, Shimamura H, Araki H, Shimotohno K.
  Source: Virology. 2004 March 1; 320(1): 135-43.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15003869

- **Dynamics of hepatitis C virus infection.**
  Author(s): Zeuzem S, Herrmann E.
  Source: Ann Hepatol. 2002 April-June; 1(2): 56-63. Review.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15115969

- **Dynamics of hepatitis C virus quasispecies turnover during interferon-alpha treatment.**
  Author(s): von Wagner M, Lee JH, Ruster B, Kronenberger B, Sarrazin C, Roth WK, Zeuzem S.
  Source: Journal of Viral Hepatitis. 2003 November; 10(6): 413-22.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14633173

- **Dynamics of subgenomic hepatitis C virus replicon RNA levels in Huh-7 cells after exposure to nucleoside antimetabolites.**
  Author(s): Stuyver LJ, McBrayer TR, Tharnish PM, Hassan AE, Chu CK, Pankiewicz KW, Watanabe KA, Schinazi RF, Otto MJ.
  Source: Journal of Virology. 2003 October; 77(19): 10689-94.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12970456

- **E2 quasispecies specificity of hepatitis C virus association with allografts immediately after liver transplantation.**
  Author(s): Hughes MG Jr, Rudy CK, Chong TW, Smith RL, Evans HL, Iezzoni JC, Sawyer RG, Pruett TL.
  Source: Liver Transplantation : Official Publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society. 2004 February; 10(2): 208-16.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14762858

- **Effect of acute self-limited hepatitis C virus (HCV) superinfection on hepatitis B virus (HBV)-related cirrhosis. Virological features of HBV-HCV dual infection.**
  Author(s): Akuta N, Suzuki F, Kobayashi M, Tsubota A, Suzuki Y, Hosaka T, Someya T, Kobayashi M, Saitoh S, Arase Y, Ikeda K, Kumada H.
  Source: Digestive Diseases and Sciences. 2004 February; 49(2): 281-8.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15104371

- **Effect of antiviral treatment on evolution of liver steatosis in patients with chronic hepatitis C: indirect evidence of a role of hepatitis C virus genotype 3 in steatosis.**
  Author(s): Castera L, Hezode C, Roudot-Thoraval F, Lonjon I, Zafrani ES, Pawlotsky JM, Dhumeaux D.
  Source: Gut. 2004 March; 53(3): 420-4.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14960527

- **Effect of in vitro interferon-beta administration on hepatitis C virus in peripheral blood mononuclear cells as a predictive marker of clinical response to interferon treatment for chronic hepatitis C.**
  Author(s): Mochizuki K, Kagawa T, Takashimizu S, Kawazoe K, Kojima S, Nagata N, Nakano A, Nishizaki Y, Shiraishi K, Itakura M, Watanabe N, Mine T, Matsuzaki S.
  Source: World Journal of Gastroenterology : Wjg. 2004 March 1; 10(5): 733-6.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14991949

- **Effect of interaction between hepatitis C virus NS5A and NS5B on hepatitis C virus RNA replication with the hepatitis C virus replicon.**
  Author(s): Shimakami T, Hijikata M, Luo H, Ma YY, Kaneko S, Shimotohno K, Murakami S.
  Source: Journal of Virology. 2004 March; 78(6): 2738-48.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14990694

- **Effects of mutations of the initiation nucleotides on hepatitis C virus RNA replication in the cell.**
  Author(s): Cai Z, Liang TJ, Luo G.
  Source: Journal of Virology. 2004 April; 78(7): 3633-43.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15016884

- **Epistatic effects of immunoglobulin GM and KM allotypes on outcome of infection with hepatitis C virus.**
  Author(s): Pandey JP, Astemborski J, Thomas DL.
  Source: Journal of Virology. 2004 May; 78(9): 4561-5.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15078937

- **Epithelioid granulomas in a patient with hepatitis C virus.**
  Author(s): Pichardo-Bahena R, Mendez-Sanchez N.
  Source: Ann Hepatol. 2002 April-June; 1(2): 91-3.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15115975

- **Ethnic differences in polymorphisms of tumor necrosis factor-alpha, interleukin-10, and transforming growth factor-beta1 genes in patients with chronic hepatitis C virus infection.**
  Author(s): Zein NN, Germer JJ, El-Zayadi AR, Vidigal PG.
  Source: The American Journal of Tropical Medicine and Hygiene. 2004 April; 70(4): 434-7.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15100460

- **Evaluation of a new NASBA assay for the qualitative detection of hepatitis C virus based on the NucliSens Basic Kit reagents.**
  Author(s): Guichon A, Chiparelli H, Martinez A, Rodriguez C, Trento A, Russi JC, Carballal G.
  Source: Journal of Clinical Virology : the Official Publication of the Pan American Society for Clinical Virology. 2004 February; 29(2): 84-91.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14747025

- **Evaluation of loss of heterozygosity before and after interferon therapy in patients with hepatitis C virus infection who developed hepatocellular carcinoma during follow up.**
  Author(s): Suzuki S, Kondo Y, Hirashima N, Kato H, Sugauchi F, Tanaka Y, Orito E, Yang Y, Shen Y, Sakakibara K, Ueda R, Mizokami M.
  Source: Journal of Gastroenterology and Hepatology. 2003 December; 18(12): 1364-72.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14675264

- **Evidence for association between hepatitis C virus seropositivity and coronary artery disease.**
  Author(s): Vassalle C, Masini S, Bianchi F, Zucchelli GC.
  Source: Heart (British Cardiac Society). 2004 May; 90(5): 565-6.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15084562

- **Evolution of hepatitis C virus variants following blood transfusion from one infected donor to several recipients: a long-term follow-up.**
  Author(s): Love A, Molnegren V, Mansson AS, Smaradottir A, Thorsteinsson SB, Widell A.
  Source: The Journal of General Virology. 2004 February; 85(Pt 2): 441-50.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14769902

- **Evolution of naturally occurring 5' non-translated region variants of hepatitis C virus genotype 1b in selectable replicons.**
  Author(s): van Leeuwen HC, Reusken CB, Roeten M, Dalebout TJ, Riezu-Boj JI, Ruiz J, Spaan WJ.
  Source: The Journal of General Virology. 2004 July; 85(Pt 7): 1859-66.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15218170

- **Examination of the relationship between the hepatitis C virus and Behcet's disease.**
  Author(s): Sonmezoglu M, Dervis E, Badur S, Yenen OS.
  Source: The Journal of Dermatology. 2004 May; 31(5): 442-3.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15187319

- **Experimental demonstration of hepatitis C virus (HCV) in an Egyptian strain of Culex pipiens complex.**
  Author(s): Hassan MI, Mangoud AM, Etewa S, Amin I, Morsy TA, El Hady G, El Besher ZM, Hammad K.
  Source: J Egypt Soc Parasitol. 2003 August; 33(2): 373-84.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14964652

- **Expression of hepatitis C virus core protein impairs DNA repair in human hepatoma cells.**
  Author(s): van Pelt JF, Severi T, Crabbe T, Eetveldt AV, Verslype C, Roskams T, Fevery J.
  Source: Cancer Letters. 2004 June 25; 209(2): 197-205.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15159022

- **Expression of hepatitis C virus core protein inhibits interferon-induced nuclear import of STATs.**
  Author(s): Melen K, Fagerlund R, Nyqvist M, Keskinen P, Julkunen I.
  Source: Journal of Medical Virology. 2004 August; 73(4): 536-47.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15221897

- **Expression of hepatitis C virus E2 ectodomain in E. coli and its application in the detection of anti-E2 antibodies in human sera.**
  Author(s): Liu J, Zhang XX, Zhang SY, Lu M, Kong YY, Wang Y, Li GD.
  Source: Acta Biochim Biophys Sin (Shanghai). 2004 January; 36(1): 57-63.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14732877

- **Extended human leukocyte antigen haplotype EH18.1 influences progression to hepatocellular carcinoma in patients with hepatitis C virus infection.**
  Author(s): Lopez-Vazquez A, Rodrigo L, Mina-Blanco A, Martinez-Borra J, Fuentes D, Rodriguez M, Perez R, Gonzalez S, Lopez-Larrea C.
  Source: The Journal of Infectious Diseases. 2004 March 15; 189(6): 957-63. Epub 2004 Mar 02.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14999597

- **Factor V Leiden polymorphism and the rate of fibrosis development in chronic hepatitis C virus infection.**
  Author(s): Wright M, Goldin R, Hellier S, Knapp S, Frodsham A, Hennig B, Hill A, Apple R, Cheng S, Thomas H, Thursz M.
  Source: Gut. 2003 August; 52(8): 1206-10.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12865283

- **Factors associated with hepatitis C virus infection in injection and noninjection drug users in Italy.**
  Author(s): Quaglio G, Lugoboni F, Pajusco B, Sarti M, Talamini G, Lechi A, Mezzelani P, Des Jarlais DC.
  Source: Clinical Infectious Diseases : an Official Publication of the Infectious Diseases Society of America. 2003 July 1; 37(1): 33-40. Epub 2003 June 24.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12830406

- **Factors that influence the severity of recurrent hepatitis C virus following liver transplantation.**
  Author(s): Porter SB, Reddy KR.
  Source: Clinics in Liver Disease. 2003 August; 7(3): 603-14. Review.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14509529

- **Failure to diagnose recent hepatitis C virus infections in London injecting drug users.**
  Author(s): Aarons E, Grant P, Soldan K, Luton P, Tang J, Tedder R.
  Source: Journal of Medical Virology. 2004 August; 73(4): 548-53.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15221898

- **Fatty change in human hepatocellular carcinoma cell lines derived from patients with antibodies to hepatitis C virus.**
  Author(s): Seki S, Kitada T, Kawada N, Kadoya H, Sakaguchi H, Nakatani K, Satake K.
  Source: Hepatogastroenterology. 2002 March-April; 49(44): 340-4.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=11995446

- **Fcgamma receptor-like activity of hepatitis C virus core protein.**
  Author(s): Maillard P, Lavergne JP, Siberil S, Faure G, Roohvand F, Petres S, Teillaud JL, Budkowska A.
  Source: The Journal of Biological Chemistry. 2004 January 23; 279(4): 2430-7. Epub 2003 November 10.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14610077

- **Features of the CD4+ T-cell response in liver and peripheral blood of hepatitis C virus-infected patients with persistently normal and abnormal alanine aminotransferase levels.**
  Author(s): Rico MA, Quiroga JA, Subira D, Garcia E, Castanon S, Sallberg M, Leroux-Roels G, Weiland O, Pardo M, Carreno V.
  Source: Journal of Hepatology. 2002 March; 36(3): 408-16.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=11867186

- **Fibrosing cholestatic hepatitis in a liver transplant recipient with hepatitis C virus infection: a case report.**
  Author(s): Furuta K, Takahashi T, Aso K, Hoshino H, Sato K, Kakita A.
  Source: Transplantation Proceedings. 2003 February; 35(1): 389-91.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12591454

- **Fibrosing cholestatic hepatitis-like syndrome in a hepatitis B virus and hepatitis C virus-negative renal transplant recipient: a case report with autopsy findings.**
  Author(s): Duseja A, Nada R, Kalra N, Acharya SK, Minz M, Joshi K, Chawla Y.
  Source: Trop Gastroenterol. 2003 January-March; 24(1): 31-4.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12974214

- **Fibrosis progression in chronic hepatitis C virus infection.**
  Author(s): McCaughan GW, George J.
  Source: Gut. 2004 March; 53(3): 318-21. Review.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14960506

- **Focal liver lesions in non-Hodgkin's lymphoma: investigation of their prevalence, clinical significance and the role of Hepatitis C virus infection.**
  Author(s): Civardi G, Vallisa D, Berte R, Lazzaro A, Moroni CF, Cavanna L.
  Source: European Journal of Cancer (Oxford, England : 1990). 2002 December; 38(18): 2382-7.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12460782

- **Follow-up of six blood donors highlights the complementary role and limitations of hepatitis C virus antibody and nucleic acid amplification tests.**
  Author(s): Hyland C, Seed CR, Kiely P, Parker S, Cowley N, Bolton W.
  Source: Vox Sanguinis. 2003 July; 85(1): 1-8.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12823724

- **Frequency and phenotype of circulating Valpha24/Vbeta11 double-positive natural killer T cells during hepatitis C virus infection.**
  Author(s): Lucas M, Gadola S, Meier U, Young NT, Harcourt G, Karadimitris A, Coumi N, Brown D, Dusheiko G, Cerundolo V, Klenerman P.
  Source: Journal of Virology. 2003 February; 77(3): 2251-7.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12525661

- **Frequency of antibodies against the hepatitis C virus in patients with hepatic cirrhosis in Yucatan, Mexico.**
  Author(s): Gongora-Biachi RA, Castro-Sansores CJ, Gonzalez-Martinez P, Lara-Perera DM, Garrido-Palma J, Lara-Perera V.
  Source: Salud Publica De Mexico. 2003 September-October; 45(5): 346-50.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14628613

- **Frequent compartmentalization of hepatitis C virus variants in circulating B cells and monocytes.**
  Author(s): Ducoulombier D, Roque-Afonso AM, Di Liberto G, Penin F, Kara R, Richard Y, Dussaix E, Feray C.
  Source: Hepatology (Baltimore, Md.). 2004 March; 39(3): 817-25.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14999702

- **Frequent loss of p53 codon 72 Pro variant in hepatitis C virus-positive carriers with hepatocellular carcinoma.**
  Author(s): Anzola M, Cuevas N, Lopez-Martinez M, Saiz A, Burgos JJ, de Pancorbo MM.
  Source: Cancer Letters. 2003 April 25; 193(2): 199-205.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12706878

- **Frequent recovery and broad genotype 2 diversity characterize hepatitis C virus infection in Ghana, West Africa.**
  Author(s): Candotti D, Temple J, Sarkodie F, Allain JP.
  Source: Journal of Virology. 2003 July; 77(14): 7914-23.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12829831

- **Full-length core sequence dependent complex-type glycosylation of hepatitis C virus E2 glycoprotein.**
  Author(s): Zhu LX, Liu J, Li YC, Kong YY, Staib C, Sutter G, Wang Y, Li GD.
  Source: World Journal of Gastroenterology : Wjg. 2002 June; 8(3): 499-504.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12046079

- **Gene expression of NS5a strong antigenic regions of hepatitis C virus in E.coli and detection of their antigenicity.**
  Author(s): Dou XG, Feng GH, Shi LL, Fields H.
  Source: Hepatobiliary Pancreat Dis Int. 2002 August; 1(3): 383-7.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14607711

- **Gene expression profile linked to p53 status in hepatitis C virus-related hepatocellular carcinoma.**
  Author(s): Okada T, Iizuka N, Yamada-Okabe H, Mori N, Tamesa T, Takemoto N, Tangoku A, Hamada K, Nakayama H, Miyamoto T, Uchimura S, Hamamoto Y, Oka M.
  Source: Febs Letters. 2003 December 18; 555(3): 583-90.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14675778

- **Gene expression profiling of the cellular transcriptional network regulated by alpha/beta interferon and its partial attenuation by the hepatitis C virus nonstructural 5A protein.**
  Author(s): Geiss GK, Carter VS, He Y, Kwieciszewski BK, Holzman T, Korth MJ, Lazaro CA, Fausto N, Bumgarner RE, Katze MG.
  Source: Journal of Virology. 2003 June; 77(11): 6367-75.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12743294

- **Generalized pustular psoriasis and Hepatitis C virus infection.**
  Author(s): Ujiie H, Shimizu T, Shimizu H.
  Source: Acta Virol. 2004; 48(1): 63-4. No Abstract Available.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15230478

- **Genetic evolution of structural region of hepatitis C virus in primary infection.**
  Author(s): Chen S, Wang YM.
  Source: World Journal of Gastroenterology : Wjg. 2002 August; 8(4): 686-93.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12174379

- **Genetic heterogeneity of hepatitis C virus (HCV) in clinical strains of HIV positive and HIV negative patients chronically infected with HCV genotype 3a.**
  Author(s): Bagaglio S, Bruno R, Lodrini S, De Mitri MS, Andreone P, Loggi E, Galli L, Lazzarin A, Morsica G.
  Source: J Biol Regul Homeost Agents. 2003 April-June; 17(2): 153-61.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14518715

- **Genetic heterogeneity of the envelope 2 gene and eradication of hepatitis C virus after a second course of interferon-alpha.**
  Author(s): Boulestin A, Sandres-Saune K, Payen JL, Alric L, Dubois M, Pasquier C, Vinel JP, Pascal JP, Puel J, Izopet J.
  Source: Journal of Medical Virology. 2002 October; 68(2): 221-8.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12210411

- **Genetic heterogeneity of the NS5A gene of hepatitis C virus and early response to interferon-alpha.**
  Author(s): Boulestin A, Sandres-Saune K, Payen JL, Rostaing L, Pasquier C, Izopet J.
  Source: The Journal of Infectious Diseases. 2003 November 1; 188(9): 1367-70. Epub 2003 October 13.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14593596

- **Genetic variability of hepatitis C virus non-structural protein 3 and virus-specific CD8+ response in patients with chronic hepatitis C.**
  Author(s): Lopez-Labrador FX, He XS, Berenguer M, Cheung RC, Gonzalez-Candelas F, Wright TL, Greenberg HB.
  Source: Journal of Medical Virology. 2004 April; 72(4): 575-85.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14981760

- **Genetic variability of hepatitis C virus NS3 protein in human leukocyte antigen-A2 liver transplant recipients with recurrent hepatitis C.**
  Author(s): Lopez-Labrador FX, Berenguer M, Sempere A, Prieto M, Sirera R, Gonzalez-Molina A, Ortiz V, Marty ML, Berenguer J, Gobernado M.
  Source: Liver Transplantation : Official Publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society. 2004 February; 10(2): 217-27.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14762859

- **Genomic and antigenomic chains of hepatitis C virus and hepatitis G virus in serum, liver and peripheral blood mononuclear cells.**
  Author(s): Torres C, Munoz de Rueda P, Ruiz-Extremera A, Quintero D, Palacios A, Salmeron J.
  Source: Rev Esp Enferm Dig. 2002 November; 94(11): 659-68. English, Spanish.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12690989

- **Genomic and phylogenetic analysis of hepatitis C virus isolates: a survey of 535 strains circulating in southern France.**
  Author(s): Tamalet C, Colson P, Tissot-Dupont H, Henry M, Tourres C, Tivoli N, Botta D, Ravaux I, Poizot-Martin I, Yahi N.
  Source: Journal of Medical Virology. 2003 November; 71(3): 391-8.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12966544

- **Genotype 2a hepatitis C virus subgenomic replicon can replicate in HepG2 and IMY-N9 cells.**
  Author(s): Date T, Kato T, Miyamoto M, Zhao Z, Yasui K, Mizokami M, Wakita T.
  Source: The Journal of Biological Chemistry. 2004 May 21; 279(21): 22371-6. Epub 2004 February 26.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14990575

- **Genotype and subtype analyses of hepatitis B virus (HBV) and possible co-infection of HBV and hepatitis C virus (HCV) or hepatitis D virus (HDV) in blood donors, patients with chronic liver disease and patients on hemodialysis in Surabaya, Indonesia.**
  Author(s): Lusida MI, Surayah, Sakugawa H, Nagano-Fujii M, Soetjipto, Mulyanto, Handajani R, Boediwarsono, Setiawan PB, Nidom CA, Ohgimoto S, Hotta H.
  Source: Microbiology and Immunology. 2003; 47(12): 969-75.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14695447

- **Genotype distribution of hepatitis C virus in the Hungarian population with chronic viral hepatitis C.**
  Author(s): Gervain J, Simon Jr G, Simon J; Hungarian Viral Hepatitis Group.
  Source: European Journal of Gastroenterology & Hepatology. 2003 April; 15(4): 449-50.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12655271

- **Genotypes of hepatitis C virus circulating in Tunisia.**
  Author(s): Djebbi A, Triki H, Bahri O, Cheikh I, Sadraoui A, Ben Ammar A, Dellagi K.
  Source: Epidemiology and Infection. 2003 June; 130(3): 501-5.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12825736

- **Genotyping of hepatitis C virus-comparison of three assays.**
  Author(s): Haushofer AC, Berg J, Hauer R, Trubert-Exinger D, Stekel HG, Kessler HH.
  Source: Journal of Clinical Virology : the Official Publication of the Pan American Society for Clinical Virology. 2003 August; 27(3): 276-85.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12878092

- **Glycosylation of hepatitis C virus envelope proteins.**
  Author(s): Goffard A, Dubuisson J.
  Source: Biochimie. 2003 March-April; 85(3-4): 295-301. Review.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12770768

- **Granulocyte and monocyte adsorptive apheresis for patients with chronic hepatitis C virus infection: a report on six cases with high plasma viremia.**
  Author(s): Sawada K, Ohnishi K, Fukunaga K, Kusaka T, Ohdo M, Nagase K, Shimoyama T, Hada T.
  Source: Ther Apher Dial. 2003 December; 7(6): 547-53.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15018242

- **Guidelines for laboratory testing and result reporting of antibody to hepatitis C virus. Centers for Disease Control and Prevention.**
  Author(s): Ann Intern Med. 2003 Feb 18;138(4):I52
  Source: Mmwr. Recommendations and Reports : Morbidity and Mortality Weekly Report. Recommendations and Reports / Centers for Disease Control. 2003 February 7; 52(Rr-3): 1-13, 15; Quiz Ce1-4.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12585851

- **Hemochromatosis (HFE) gene mutations and hepatitis C virus infection as risk factors for porphyria cutanea tarda in Hungarian patients.**
  Author(s): Nagy Z, Koszo F, Par A, Emri G, Horkay I, Horanyi M, Karadi O, Rumi G Jr, Morvay M, Varga V, Dobozy A, Mozsik G.
  Source: Liver International : Official Journal of the International Association for the Study of the Liver. 2004 February; 24(1): 16-20.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15101996

- **Hepatitis C virus (HCV) relapses after anti-HCV therapy are more frequent in HIV-infected patients.**
  Author(s): Soriano V, Perez-Olmeda M, Rios P, Nunez M, Garcia-Samaniego J, Gonzalez-Lahoz J.
  Source: Aids Research and Human Retroviruses. 2004 April; 20(4): 351-3.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15157353

- **Hepatitis C virus and dental personnel.**
  Author(s): Palenik CJ.
  Source: Dent Today. 2004 May; 23(5): 56-9. No Abstract Available.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15164474

- **Hepatitis C virus and rheumatoid arthritis: further pieces to the puzzle.**
  Author(s): Csepregi A, Poor G, Nemesanszky E.
  Source: The Journal of Rheumatology. 2004 May; 31(5): 1016-7.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15124282

- **Hepatitis C virus coinfection in a cohort of HIV-infected individuals from Santos, Brazil: seroprevalence and associated factors.**
  Author(s): Segurado AC, Braga P, Etzel A, Cardoso MR.
  Source: Aids Patient Care and Stds. 2004 March; 18(3): 135-43.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15104874

- **Hepatitis C virus in patients with non-Hodgkin's lymphoma in southeastern Anatolia region of Turkey: a prospective case-control study of 119 patients.**
  Author(s): Isikdogan A, Ayyildiz O, Dursun M, Tiftik N, Batun S, Muftuoglu E.
  Source: Leukemia & Lymphoma. 2003 October; 44(10): 1745-7.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14692528

- **Hepatitis C virus infection and non-Hodgkin lymphoma: results of the NCI-SEER multi-center case-control study.**
  Author(s): Engels EA, Chatterjee N, Cerhan JR, Davis S, Cozen W, Severson RK, Whitby D, Colt JS, Hartge P.
  Source: International Journal of Cancer. Journal International Du Cancer. 2004 August 10; 111(1): 76-80.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15185346

- **Hepatitis C virus infection at Sharkia Governorate, Egypt: seroprevalence and associated risk factors.**
  Author(s): el-Sadawy M, Ragab H, el-Toukhy H, el-Mor Ael-L, Mangoud AM, Eissa MH, Afefy AF, el-Shorbagy E, Ibrahem IA, Mahrous S, Abdel-Monem A, Sabee EI, Ismail A, Morsy TA, Etewa S, Nor Edin E, Mostafa Y, Abouel-Magd Y, Hassan MI, Lakouz K, Abdel-Aziz K, el-Hady G, Saber M.
  Source: J Egypt Soc Parasitol. 2004 April; 34(1 Suppl): 367-84.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15124747

- **Hepatitis C virus infection in dialysis and chronic liver patients: Viraemia dependent anti-E2-antibody response.**
  Author(s): Hanuka N, Sikuler E, Tovbin D, Neville L, Nussbaum O, Mostoslavsky M, Orgel M, Yaari A, Manor S, Dagan S, Hilzenrat N, Shemer-Avni Y.
  Source: Journal of Medical Virology. 2004 August; 73(4): 529-35.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15221896

- **Hepatitis C virus persistence after spontaneous or treatment-induced resolution of hepatitis C.**
  Author(s): Pham TN, MacParland SA, Mulrooney PM, Cooksley H, Naoumov NV, Michalak TI.
  Source: Journal of Virology. 2004 June; 78(11): 5867-74.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15140984

- **Hepatitis C virus quasi-species dynamics predict progression of fibrosis after liver transplantation.**
  Author(s): Arenas JI, Gallegos-Orozco JF, Laskus T, Wilkinson J, Khatib A, Fasola C, Adair D, Radkowski M, Kibler KV, Nowicki M, Douglas D, Williams J, Netto G, Mulligan D, Klintmalm G, Rakela J, Vargas HE.
  Source: The Journal of Infectious Diseases. 2004 June 1; 189(11): 2037-46. Epub 2004 May 10.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15143471

- **Hepatitis C virus RNA level changes in sera during different regimens of treatment in patients with chronic hepatitis C.**
  Author(s): Mazur W, Gonciarz M, Mazurek U, Jurzak M, Wilczok T, Gonciarz Z.
  Source: Medical Science Monitor : International Medical Journal of Experimental and Clinical Research. 2003 August; 9 Suppl 3: 39-43.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15156611

- **Hepatitis C virus subgenomic replicons in the human embryonic kidney 293 cell line.**
  Author(s): Ali S, Pellerin C, Lamarre D, Kukolj G.
  Source: Journal of Virology. 2004 January; 78(1): 491-501.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14671129

- **Hepatitis C virus targets DC-SIGN and L-SIGN to escape lysosomal degradation.**
  Author(s): Ludwig IS, Lekkerkerker AN, Depla E, Bosman F, Musters RJ, Depraetere S, van Kooyk Y, Geijtenbeek TB.
  Source: Journal of Virology. 2004 August; 78(15): 8322-32.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15254204

- **Hepatitis C virus: simply too smart to be just a liver pathogen.**
  Author(s): Mondelli MU.
  Source: Dig Liver Dis. 2003 November; 35(11): 760-2. No Abstract Available.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14674664

- **Hepatitis C virus-associated pericardial effusion and tamponade in a liver transplant recipient.**
  Author(s): Nikolaidis LA, Azzouz M, Friedlander L, Van Thiel DH, Gradman AH.
  Source: The Canadian Journal of Cardiology. 2004 May 15; 20(7): 719-21.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15197425

- **HIV and hepatitis C virus co-infection.**
  Author(s): Rockstroh JK, Spengler U.
  Source: The Lancet Infectious Diseases. 2004 July; 4(7): 437-44. Review.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15219554

- **HIV and HHV-8 negative primary effusion lymphoma in a patient with hepatitis C virus-related liver cirrhosis.**
  Author(s): Paner GP, Jensen J, Foreman KE, Reyes CV.
  Source: Leukemia & Lymphoma. 2003 October; 44(10): 1811-4. Review.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14692539

- **Human immunodeficiency virus (HIV) and hepatitis C virus (HCV) in a Northern Alberta population.**
  Author(s): Bowker SL, Soskolne CL, Houston SC, Newman SC, Jhangri GS.
  Source: Canadian Journal of Public Health. Revue Canadienne De Sante Publique. 2004 May-June; 95(3): 188-92.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15191121

- **Human monoclonal antibody to hepatitis C virus E1 glycoprotein that blocks virus attachment and viral infectivity.**
  Author(s): Keck ZY, Sung VM, Perkins S, Rowe J, Paul S, Liang TJ, Lai MM, Foung SK.
  Source: Journal of Virology. 2004 July; 78(13): 7257-63.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15194801

- **Identification of novel hepatitis C virus-specific cytotoxic T lymphocyte epitopes by ELISpot assay using peptides with human leukocyte antigen-A*2402-binding motifs.**
  Author(s): Hakamada T, Funatsuki K, Morita H, Ugajin T, Nakamura I, Ishiko H, Matsuzaki Y, Tanaka N, Imawari M.
  Source: The Journal of General Virology. 2004 June; 85(Pt 6): 1521-31.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15166436

- **Identification of unique hepatitis C virus quasispecies in the central nervous system and comparative analysis of internal translational efficiency of brain, liver, and serum variants.**
  Author(s): Forton DM, Karayiannis P, Mahmud N, Taylor-Robinson SD, Thomas HC.
  Source: Journal of Virology. 2004 May; 78(10): 5170-83.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15113899

- **IL-23 induces stronger sustained CTL and Th1 immune responses than IL-12 in hepatitis C virus envelope protein 2 DNA immunization.**
  Author(s): Ha SJ, Kim DJ, Baek KH, Yun YD, Sung YC.
  Source: Journal of Immunology (Baltimore, Md. : 1950). 2004 January 1; 172(1): 525-31.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14688363

- **Immune-based novel therapies for chronic hepatitis C virus infection.**
  Author(s): Kakimi K.
  Source: Hum Cell. 2003 December; 16(4): 191-7. Review.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15147039

- **Immunization with hepatitis C virus-like particles induces humoral and cellular immune responses in nonhuman primates.**
  Author(s): Jeong SH, Qiao M, Nascimbeni M, Hu Z, Rehermann B, Murthy K, Liang TJ.
  Source: Journal of Virology. 2004 July; 78(13): 6995-7003.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15194776

- **Impact of acute hepatitis C virus superinfection in patients with chronic hepatitis B virus infection.**
  Author(s): Liaw YF, Chen YC, Sheen IS, Chien RN, Yeh CT, Chu CM.
  Source: Gastroenterology. 2004 April; 126(4): 1024-9.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15057742

- **Increased responses to inhaled oxitropium bromide in asthmatic patients with active hepatitis C virus infection.**
  Author(s): Kanazawa H, Hirata K, Yoshikawa J.
  Source: Chest. 2004 April; 125(4): 1368-71.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15078747

- **Induced oxidative stress and activated expression of manganese superoxide dismutase during hepatitis C virus replication: role of JNK, p38 MAPK and AP-1.**
  Author(s): Qadri I, Iwahashi M, Capasso JM, Hopken MW, Flores S, Schaack J, Simon FR.
  Source: The Biochemical Journal. 2004 March 15; 378(Pt 3): 919-28.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14670077

- **Infection with hepatitis C virus genotype 4 in the United States.**
  Author(s): Lyra AC, Ramrakhiani S, Bacon BR, Di Bisceglie AM.
  Source: Journal of Clinical Gastroenterology. 2004 January; 38(1): 68-71.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14679330

- **Infection with hepatitis C virus transmitted by accidental needlesticks.**
  Author(s): De Carli G, Puro V, Scognamiglio P, Ippolito G; Studio Italiano Rischio Occupazionale da HIV; European Group for the Standardization of the Management of Occupational Exposure to HIV/Blood-Borne Infections.
  Source: Clinical Infectious Diseases : an Official Publication of the Infectious Diseases Society of America. 2003 December 15; 37(12): 1718-9; Discussion 1719.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14689357

- **Infection with human herpes virus type 8 in an area at high prevalence for hepatitis C virus infection in southern Italy.**
  Author(s): Montella M, Serraino D, Crispo A, Romano N, Fusco M, Goedert JJ.
  Source: Journal of Viral Hepatitis. 2004 May; 11(3): 268-70.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15117330

- **Influence of N-linked glycans on intracellular transport of hepatitis C virus E1 chimeric glycoprotein and its role in pseudotype virus infectivity.**
  Author(s): Beyene A, Basu A, Meyer K, Ray R.
  Source: Virology. 2004 July 1; 324(2): 273-85.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15207615

- **Insertion of green fluorescent protein into nonstructural protein 5A allows direct visualization of functional hepatitis C virus replication complexes.**
  Author(s): Moradpour D, Evans MJ, Gosert R, Yuan Z, Blum HE, Goff SP, Lindenbach BD, Rice CM.
  Source: Journal of Virology. 2004 July; 78(14): 7400-9.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15220413

- **Interest of transjugular liver biopsy in adult patients with haemophilia or other congenital bleeding disorders infected with hepatitis C virus.**
  Author(s): Stieltjes N, Ounnoughene N, Sava E, Paugy P, Roussel-Robert V, Rosenberg AR, Terris B, Salmon-Ceron D, Sogni P.
  Source: British Journal of Haematology. 2004 June; 125(6): 769-76.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15180867

- **Interpretation of undetectable hepatitis C virus RNA levels in HIV-hepatitis C virus co-infection.**
  Author(s): Cooper CL, Cameron DW.
  Source: Aids (London, England). 2004 January 23; 18(2): 337-8.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15075557

- **Interspousal transmission of hepatitis C virus: application of comparing the variability of HVR1 nucleotide region.**
  Author(s): Lai KW, Young KC, Cheng PN, Chen SH, Chang TT.
  Source: Hepatogastroenterology. 2004 May-June; 51(57): 791-5.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15143918

- **Intracellular inhibition of hepatitis C virus (HCV) internal ribosomal entry site (IRES)-dependent translation by peptide nucleic acids (PNAs) and locked nucleic acids (LNAs).**
  Author(s): Nulf CJ, Corey D.
  Source: Nucleic Acids Research. 2004 July 19; 32(13): 3792-8. Print 2004.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15263060

- **Intra-hepatic messenger RNA levels for interferons and related genes in hepatitis C virus/HIV co-infected patients.**
  Author(s): Abbate I, Cappiello G, Rosati S, Tocci G, Antonucci G, Solmone M, Longo R, Spano A, Capobianchi MR.
  Source: Aids (London, England). 2004 March 5; 18(4): 691-2.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15090776

- **Intramembrane proteolysis and endoplasmic reticulum retention of hepatitis C virus core protein.**
  Author(s): Okamoto K, Moriishi K, Miyamura T, Matsuura Y.
  Source: Journal of Virology. 2004 June; 78(12): 6370-80.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15163730

- **Involvement of the CXCL12/CXCR4 pathway in the advanced liver disease that is associated with hepatitis C virus or hepatitis B virus.**
  Author(s): Wald O, Pappo O, Safadi R, Dagan-Berger M, Beider K, Wald H, Franitza S, Weiss I, Avniel S, Boaz P, Hanna J, Zamir G, Eid A, Mandelboim O, Spengler U, Galun E, Peled A.
  Source: European Journal of Immunology. 2004 April; 34(4): 1164-74.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15048728

- **Kidney transplantation from hepatitis C virus positive donors.**
  Author(s): Rozental R, Bicans J, Shevelev V, Trushkov S, Amerika D.
  Source: Transplantation Proceedings. 2002 November; 34(7): 2581.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12431531

- **Kinetics and significance of serum hepatitis C virus core antigen in patients with acute hepatitis C.**
  Author(s): Cividini A, Cerino A, Muzzi A, Furione M, Rebucci C, Segagni L, Gatti M, Barnaba V, Mondelli MU.
  Source: Journal of Clinical Microbiology. 2003 May; 41(5): 2144-6.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12734263

- **Kinetics of CD4+ and CD8+ memory T-cell responses during hepatitis C virus rechallenge of previously recovered chimpanzees.**
  Author(s): Nascimbeni M, Mizukoshi E, Bosmann M, Major ME, Mihalik K, Rice CM, Feinstone SM, Rehermann B.
  Source: Journal of Virology. 2003 April; 77(8): 4781-93.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12663785

- **Kinetics of hepatitis C virus load during hemodialysis: novel perspectives.**
  Author(s): Fabrizi F, Bunnapradist S, Lunghi G, Martin P.
  Source: Journal of Nephrology. 2003 July-August; 16(4): 467-75. Review.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14696748

- **Kinetics of intrahepatic hepatitis C virus (HCV)-specific CD4+ T cell responses in HCV and Schistosoma mansoni coinfection: relation to progression of liver fibrosis.**
  Author(s): Kamal SM, Graham CS, He Q, Bianchi L, Tawil AA, Rasenack JW, Khalifa KA, Massoud MM, Koziel MJ.
  Source: The Journal of Infectious Diseases. 2004 April 1; 189(7): 1140-50. Epub 2004 March 12.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15031780

- **Laboratory evaluation of a fully automated chemiluminescence immunoassay for rapid detection of HBsAg, antibodies to HBsAg, and antibodies to hepatitis C virus.**
  Author(s): Ismail N, Fish GE, Smith MB.
  Source: Journal of Clinical Microbiology. 2004 February; 42(2): 610-7.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14766824

- **Lack of association between hepatitis C virus and oral epithelial dysplasia in British patients.**
  Author(s): Jaber MA, Porter SR, Bain L, Scully C.
  Source: International Journal of Oral and Maxillofacial Surgery. 2003 April; 32(2): 181-3.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12729779

- **Lack of behavior change after disclosure of hepatitis C virus infection among young injection drug users in Baltimore, Maryland.**
  Author(s): Ompad DC, Fuller CM, Vlahov D, Thomas D, Strathdee SA.
  Source: Clinical Infectious Diseases : an Official Publication of the Infectious Diseases Society of America. 2002 October 1; 35(7): 783-8. Epub 2002 September 03.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12228813

- **Lack of clinical significance of variability in the internal ribosome entry site of hepatitis C virus.**
  Author(s): Thelu MA, Drouet E, Hilleret MN, Zarski JP.
  Source: Journal of Medical Virology. 2004 March; 72(3): 396-405.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14748063

- **Lack of epidemiological evidence for a role of resolved hepatitis B virus infection in hepatocarcinogenesis in patients infected with hepatitis C virus in Japan.**
  Author(s): Hiraoka T, Katayama K, Tanaka J, Ohno N, Joko K, Komiya Y, Kumagai J, Mizui M, Hino K, Miyakawa Y, Yoshizawa H.
  Source: Intervirology. 2003; 46(3): 171-6.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12867755

- **Lack of in vivo blockade of Fas- and TNFR1-mediated hepatocyte apoptosis by the hepatitis C virus.**
  Author(s): Rubbia-Brandt L, Taylor S, Gindre P, Quadri R, Abid K, Spahr L, Negro F.
  Source: The Journal of Pathology. 2002 August; 197(5): 617-23.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12210081

- **Lack of phenotypic and functional impairment in dendritic cells from chimpanzees chronically infected with hepatitis C virus.**
  Author(s): Larsson M, Babcock E, Grakoui A, Shoukry N, Lauer G, Rice C, Walker C, Bhardwaj N.
  Source: Journal of Virology. 2004 June; 78(12): 6151-61.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15163708

- **Lichen planus and hepatitis C virus infection.**
  Author(s): Gimenez-Garcia R, Perez-Castrillon JL.
  Source: Journal of the European Academy of Dermatology and Venereology : Jeadv. 2003 May; 17(3): 291-5.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12702068

- **Lichen sclerosus-lichen planus overlap in a patient with hepatitis C virus infection.**
  Author(s): Yashar S, Han KF, Haley JC.
  Source: The British Journal of Dermatology. 2004 January; 150(1): 168-9.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14746647

- **Liver biopsy, viral kinetics, and the impact of viremia on severity of hepatitis C virus recurrence.**
  Author(s): Charlton M.
  Source: Liver Transplantation : Official Publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society. 2003 November; 9(11): S58-62. Review.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14586897

- **Liver transplantation in a patient coinfected with human immunodeficiency virus and hepatitis C virus.**
  Author(s): Gonzalez Alonso R, Barcena R, Blesa C, Garcia M, Moreno A, Fortun J, Martin P, Quereda C, de Vicente E.
  Source: Transplantation Proceedings. 2003 August; 35(5): 1846-7.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12962819

- **Liver transplantation in hepatitis C virus-related cirrhosis.**
  Author(s): Ziolkowski J, Niewczas M, Senatorski G, Zygier D, Oldakowska-Jedynak U, Wyzgal J, Michalska W, Niemczyk M, Zieniewicz K, Nyckowski P, Alsharabi A, Hevelke P, Krawczyk M, Gornicka B, Ziarkiewicz-Wroblewska B, Paczek L.
  Source: Transplantation Proceedings. 2003 September; 35(6): 2275-7.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14529913

- **Liver transplantation with hepatitis C virus-infected graft: interaction between donor and recipient viral strains.**
  Author(s): Fan X, Lang DM, Xu Y, Lyra AC, Yusim K, Everhart JE, Korber BT, Perelson AS, Di Bisceglie AM.
  Source: Hepatology (Baltimore, Md.). 2003 July; 38(1): 25-33.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12829983

- **Localization of hepatitis C virus in gastrointestinal mucosa: a possible reservoir for relapse.**
  Author(s): Miglioresi L, Riva E, Antonelli G, Russo F, Ricci GL.
  Source: Hepatology (Baltimore, Md.). 2003 September; 38(3): 775.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12939605

- **Long-range RNA-RNA interaction between the 5' nontranslated region and the core-coding sequences of hepatitis C virus modulates the IRES-dependent translation.**
  Author(s): Kim YK, Lee SH, Kim CS, Seol SK, Jang SK.
  Source: Rna (New York, N.Y.). 2003 May; 9(5): 599-606.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12702818

- **Long-term outcome after liver transplantation in Egyptians transplanted for hepatitis C virus cirrhosis.**
  Author(s): Khalaf H.
  Source: Transplantation Proceedings. 2003 November; 35(7): 2777-8.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14612116

- **Long-term ribavirin therapy in hepatitis C virus-positive renal transplant patients: effects on renal function and liver histology.**
  Author(s): Kamar N, Sandres-Saune K, Selves J, Ribes D, Cointault O, Durand D, Izopet J, Rostaing L.
  Source: American Journal of Kidney Diseases : the Official Journal of the National Kidney Foundation. 2003 July; 42(1): 184-92.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12830471

- **Loss of hepatitis C virus RNA after parturition in female patients with chronic HCV infection.**
  Author(s): Hattori Y, Orito E, Ohno T, Sugauchi F, Suzuki S, Sugiura M, Suzumori K, Hattori K, Ueda R, Mizokami M.
  Source: Journal of Medical Virology. 2003 October; 71(2): 205-11.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12938194

- **Low incidence and prevalence of hepatitis C virus infection among sexually active non-intravenous drug-using adults, San Francisco, 1997-2000.**
  Author(s): Hammer GP, Kellogg TA, McFarland WC, Wong E, Louie B, Williams I, Dilley J, Page-Shafer K, Klausner JD.
  Source: Sexually Transmitted Diseases. 2003 December; 30(12): 919-24.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14646642

- **Low prevalence of hepatitis C virus antibodies in HIV-endemic area of Zimbabwe support sexual transmission as the major route of HIV transmission in Africa.**
  Author(s): Kallestrup P, Zinyama R, Gomo E, Dickmeiss E, Platz P, Gerstoft J, Ullum H.
  Source: Aids (London, England). 2003 June 13; 17(9): 1400-2.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12799566

- **Management of healthcare workers after occupational exposure to hepatitis C virus.**
  Author(s): Magnavita N.
  Source: The Medical Journal of Australia. 2004 February 16; 180(4): 195-6; Author Reply 196.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14960144

- **Management of patients with chronic hepatitis C virus infection and previous nonresponse.**
  Author(s): Shiffman ML.
  Source: Reviews in Gastroenterological Disorders. 2004; 4 Suppl 1: S22-30. Review.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15184821

- **Marked reduction in the prevalence of hepatitis C virus infection in hemodialysis patients: causes and consequences.**
  Author(s): Espinosa M, Martn-Malo A, Ojeda R, Santamara R, Soriano S, Aguera M, Aljama P.
  Source: American Journal of Kidney Diseases : the Official Journal of the National Kidney Foundation. 2004 April; 43(4): 685-9.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15042545

- **Mechanism of action and antiviral activity of benzimidazole-based allosteric inhibitors of the hepatitis C virus RNA-dependent RNA polymerase.**
  Author(s): Tomei L, Altamura S, Bartholomew L, Biroccio A, Ceccacci A, Pacini L, Narjes F, Gennari N, Bisbocci M, Incitti I, Orsatti L, Harper S, Stansfield I, Rowley M, De Francesco R, Migliaccio G.
  Source: Journal of Virology. 2003 December; 77(24): 13225-31.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14645579

- **Mechanisms of increased insulin resistance in non-cirrhotic patients with chronic hepatitis C virus infection.**
  Author(s): Maeno T, Okumura A, Ishikawa T, Kato K, Sakakibara F, Sato K, Ayada M, Hotta N, Tagaya T, Fukuzawa Y, Kakumu S.
  Source: Journal of Gastroenterology and Hepatology. 2003 December; 18(12): 1358-63.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14675263

- **Membrane association of hepatitis C virus nonstructural proteins and identification of the membrane alteration that harbors the viral replication complex.**
  Author(s): Moradpour D, Gosert R, Egger D, Penin F, Blum HE, Bienz K.
  Source: Antiviral Research. 2003 October; 60(2): 103-9. Review.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14638405

- **Membranoproliferative glomerulonephritis and leukocytoclastic vasculitis without cryoglobulin in chronic hepatitis C virus infection.**
  Author(s): Nakajima A, Adachi M, Tanaka M, Suwa A, Yasuki Y, Imaeda H, Inada S.
  Source: Intern Med. 2003 October; 42(10): 1042-6.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14606724

- **Meta-analysis of mutations in the NS5A gene and hepatitis C virus resistance to interferon therapy: uniting discordant conclusions.**
  Author(s): Schinkel J, Spoon WJ, Kroes AC.
  Source: Antivir Ther. 2004 April; 9(2): 275-86.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15134190

- **Metal contents in the liver of patients with chronic liver disease caused by hepatitis C virus. Reference to hepatocellular carcinoma.**
  Author(s): Ebara M, Fukuda H, Hatano R, Yoshikawa M, Sugiura N, Saisho H, Kondo F, Yukawa M.
  Source: Oncology. 2003; 65(4): 323-30.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14707452

- **Modeling viral and drug kinetics: hepatitis C virus treatment with pegylated interferon alfa-2b.**
  Author(s): Powers KA, Dixit NM, Ribeiro RM, Golia P, Talal AH, Perelson AS.
  Source: Seminars in Liver Disease. 2003; 23 Suppl 1: 13-8.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12934163

- **Modulation of p53 transcription regulatory activity and post-translational modification by hepatitis C virus core protein.**
  Author(s): Kao CF, Chen SY, Chen JY, Wu Lee YH.
  Source: Oncogene. 2004 April 1; 23(14): 2472-83.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14968111

- **Morphine enhances hepatitis C virus (HCV) replicon expression.**
  Author(s): Li Y, Zhang T, Douglas SD, Lai JP, Xiao WD, Pleasure DE, Ho WZ.
  Source: American Journal of Pathology. 2003 September; 163(3): 1167-75.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12937158

- **Multifaceted functions of B cells in chronic hepatitis C virus infection.**
  Author(s): Mondelli MU.
  Source: Antiviral Research. 2003 October; 60(2): 111-5. Review.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14638406

- **Multiplex real-time quantitative RT-PCR assay for hepatitis B virus, hepatitis C virus, and human immunodeficiency virus type 1.**
  Author(s): Candotti D, Temple J, Owusu-Ofori S, Allain JP.
  Source: Journal of Virological Methods. 2004 June 1; 118(1): 39-47.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15158067

- **Mutagenic and inhibitory effects of ribavirin on hepatitis C virus RNA polymerase.**
  Author(s): Vo NV, Young KC, Lai MM.
  Source: Biochemistry. 2003 September 9; 42(35): 10462-71.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12950173

- **Mutations in the NS5A and E2-PePHD regions of hepatitis C virus genotype 1b and response to combination therapy of interferon plus ribavirin.**
  Author(s): Yang SS, Lai MY, Chen DS, Chen GH, Kao JH.
  Source: Liver International : Official Journal of the International Association for the Study of the Liver. 2003 December; 23(6): 426-33.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14986817

- **Natural history and risk factors for progression of hepatitis C virus disease and development of hepatocellular cancer before liver transplantation.**
  Author(s): Shiffman ML.
  Source: Liver Transplantation : Official Publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society. 2003 November; 9(11): S14-20.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14586890

- **Natural history of hepatitis C virus among apparently normal schoolchildren: follow-up after 7 years.**
  Author(s): El-Sherbini A, Hassan W, Abdel-Hamid M, Naeim A.
  Source: Journal of Tropical Pediatrics. 2003 December; 49(6): 384-5.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14725420

- **Natural history of hepatitis C virus infection.**
  Author(s): Mondelli MU.
  Source: J Biol Regul Homeost Agents. 2003 April-June; 17(2): 128-32. Review.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14518710

- **Neither hepatitis C virus genotype nor virus load affects survival of patients with hepatocellular carcinoma.**
  Author(s): Akamatsu M, Yoshida H, Shiina S, Teratani T, Tateishi R, Obi S, Sato S, Koike Y, Fujishima T, Ishikawa T, Shiratori Y, Omata M.
  Source: European Journal of Gastroenterology & Hepatology. 2004 May; 16(5): 459-66.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15097037

- **Neutralising antibody, CTL and dendritic cell responses to hepatitis C virus: a preventative vaccine strategy.**
  Author(s): Torresi J, Bharadwaj M, Jackson DC, Gowans EJ.
  Source: Current Drug Targets. 2004 January; 5(1): 41-56. Review.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14738217

- **Neutralizing antibodies to hepatitis C virus (HCV) in immune globulins derived from anti-HCV-positive plasma.**
  Author(s): Yu MY, Bartosch B, Zhang P, Guo ZP, Renzi PM, Shen LM, Granier C, Feinstone SM, Cosset FL, Purcell RH.
  Source: Proceedings of the National Academy of Sciences of the United States of America. 2004 May 18; 101(20): 7705-10. Epub 2004 May 10.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15136748

- **Neutralizing antibody response during acute and chronic hepatitis C virus infection.**
  Author(s): Logvinoff C, Major ME, Oldach D, Heyward S, Talal A, Balfe P, Feinstone SM, Alter H, Rice CM, McKeating JA.
  Source: Proceedings of the National Academy of Sciences of the United States of America. 2004 July 6; 101(27): 10149-54. Epub 2004 June 25.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15220475

- **New therapies for chronic hepatitis C virus infection.**
  Author(s): Dev A, Patel K, McHutchison JG.
  Source: Current Gastroenterology Reports. 2004 February; 6(1): 77-86. Review.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14720458

- **Non-Hodgkin's lymphoma and hepatitis C virus: a case-control study from northern and southern Italy.**
  Author(s): Talamini R, Montella M, Crovatto M, Dal Maso L, Crispo A, Negri E, Spina M, Pinto A, Carbone A, Franceschi S.
  Source: International Journal of Cancer. Journal International Du Cancer. 2004 June 20; 110(3): 380-5.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15095303

- **Non-organ-specific autoantibodies in children with chronic hepatitis C virus infection.**
  Author(s): Bogdanos DP, Mieli-Vergani G, Vergani D.
  Source: Clinical Infectious Diseases : an Official Publication of the Infectious Diseases Society of America. 2004 May 15; 38(10): 1505; Author Reply 1505-6.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15156495

- **Occult hepatitis C virus infection in patients in whom the etiology of persistently abnormal results of liver-function tests is unknown.**
  Author(s): Castillo I, Pardo M, Bartolome J, Ortiz-Movilla N, Rodriguez-Inigo E, de Lucas S, Salas C, Jimenez-Heffernan JA, Perez-Mota A, Graus J, Lopez-Alcorocho JM, Carreno V.
  Source: The Journal of Infectious Diseases. 2004 January 1; 189(1): 7-14. Epub 2003 December 31.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14702147

- **Occult hepatitis C virus infection in type II mixed cryoglobulinaemia.**
  Author(s): Casato M, Lilli D, Donato G, Granata M, Conti V, Del Giudice G, Rivanera D, Scagnolari C, Antonelli G, Fiorilli M.
  Source: Journal of Viral Hepatitis. 2003 November; 10(6): 455-9.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14633180

- **Occupational exposure to hepatitis C virus infection.**
  Author(s): Ng D, Feller ER.
  Source: Medicine and Health, Rhode Island. 2003 June; 86(6): 165-7.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12973886

- **Occupational exposures to human immunodeficiency virus, hepatitis B virus, and hepatitis C virus: risk, prevention, and management.**
  Author(s): Cleveland JL, Cardo DM.
  Source: Dent Clin North Am. 2003 October; 47(4): 681-96. Review.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14664459

- **Occupational transmission of hepatitis C virus.**
  Author(s): Lunsk AJ.
  Source: Jama : the Journal of the American Medical Association. 2002 September 25; 288(12): 1469; Author Reply 1469-71.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12243629

- **Once-weekly epoetin alfa improves anemia and facilitates maintenance of ribavirin dosing in hepatitis C virus-infected patients receiving ribavirin plus interferon alfa.**
  Author(s): Dieterich DT, Wasserman R, Brau N, Hassanein TI, Bini EJ, Bowers PJ, Sulkowski MS.
  Source: The American Journal of Gastroenterology. 2003 November; 98(11): 2491-9.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14638354

- **Optimized virologic response in hepatitis C virus genotype 4 with peginterferon-alpha2a and ribavirin.**
  Author(s): Diago M, Hassanein T, Rodes J, Ackrill AM, Sedarati F.
  Source: Annals of Internal Medicine. 2004 January 6; 140(1): 72-3.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14706990

- **Outcome of kidney transplant in chronic hepatitis C virus patients: effect of pretransplantation interferon-alpha2b monotherapy.**
  Author(s): Gonzalez-Roncero F, Gentil MA, Valdivia MA, Algarra G, Pereira P, Toro J, Sayago M, Mateos J.
  Source: Transplantation Proceedings. 2003 August; 35(5): 1745-7.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12962779

- **Outcome of patients with hepatitis C virus-related single, small hepatocellular carcinoma.**
  Author(s): Sako K, Komorizono Y, Oketani M, Hasegawa S, Yamasaki N, Shibatou T, Maeda M, Kohara K, Shigenobu S, Yasunari H, Sakurai K, Hiwaki T, Ishibashi K, Arima T.
  Source: Anticancer Res. 2003 September-October; 23(5B): 4191-6.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14666624

- **Overexpression of a DEAD box/RNA helicase protein, rck/p54, in human hepatocytes from patients with hepatitis C virus-related chronic hepatitis and its implication in hepatocellular carcinogenesis.**
  Author(s): Miyaji K, Nakagawa Y, Matsumoto K, Yoshida H, Morikawa H, Hongou Y, Arisaka Y, Kojima H, Inoue T, Hirata I, Katsu K, Akao Y.
  Source: Journal of Viral Hepatitis. 2003 July; 10(4): 241-8.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12823589

- **Peginterferon Alfa-2a plus ribavirin for chronic hepatitis C virus infection in HIV-infected patients.**
  Author(s): Torriani FJ, Rodriguez-Torres M, Rockstroh JK, Lissen E, Gonzalez-Garcia J, Lazzarin A, Carosi G, Sasadeusz J, Katlama C, Montaner J, Sette H Jr, Passe S, De Pamphilis J, Duff F, Schrenk UM, Dieterich DT; APRICOT Study Group.
  Source: The New England Journal of Medicine. 2004 July 29; 351(5): 438-50.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15282351

- **Polymorphisms of NS5B protein relates to early clearance of hepatitis C virus by interferon plus ribavirin: a pilot study.**
  Author(s): Kumagai N, Takahashi N, Kinoshita M, Tsunematsu S, Tsuchimoto K, Saito H, Ishii H.
  Source: Journal of Viral Hepatitis. 2004 May; 11(3): 225-35.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15117324

- **Prevalence and clinical significance of hepatitis C virus infection in Thai patients with thalassemia.**
  Author(s): Wanachiwanawin W, Luengrojanakul P, Sirangkapracha P, Leowattana W, Fucharoen S.
  Source: International Journal of Hematology. 2003 November; 78(4): 374-8.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14686498

- **Prevention of hepatitis C virus infection.**
  Author(s): Kew M, Francois G, Lavanchy D, Margolis H, Van Damme P, Grob P, Hallauer J, Shouval D, Leroux-Roels G, Meheus A; Viral Hepatitis Prevention Board.
  Source: Journal of Viral Hepatitis. 2004 May; 11(3): 198-205. Review.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15117321

- **Primary biliary cirrhosis and hepatitis C virus infection.**
  Author(s): Floreani A, Baragiotta A, Leone MG, Baldo V, Naccarato R.
  Source: The American Journal of Gastroenterology. 2003 December; 98(12): 2757-62.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14687829

- **Prospects for dendritic cell vaccination in persistent infection with hepatitis C virus.**
  Author(s): Gowans EJ, Jones KL, Bharadwaj M, Jackson DC.
  Source: Journal of Clinical Virology : the Official Publication of the Pan American Society for Clinical Virology. 2004 August; 30(4): 283-90. Review.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15163415

- **Proteomic approach identifies HSP27 as an interacting partner of the hepatitis C virus NS5A protein.**
  Author(s): Choi YW, Tan YJ, Lim SG, Hong W, Goh PY.
  Source: Biochemical and Biophysical Research Communications. 2004 May 28; 318(2): 514-9.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15120631

- **Proteomic profiling of heat shock protein 70 family members as biomarkers for hepatitis C virus-related hepatocellular carcinoma.**
  Author(s): Takashima M, Kuramitsu Y, Yokoyama Y, Iizuka N, Toda T, Sakaida I, Okita K, Oka M, Nakamura K.
  Source: Proteomics. 2003 December; 3(12): 2487-93.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14673798

- **Pseudotype hepatitis C virus enters immature myeloid dendritic cells through the interaction with lectin.**
  Author(s): Kaimori A, Kanto T, Kwang Limn C, Komoda Y, Oki C, Inoue M, Miyatake H, Itose I, Sakakibara M, Yakushijin T, Takehara T, Matsuura Y, Hayashi N.
  Source: Virology. 2004 June 20; 324(1): 74-83.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15183055

- **PSG consensus statement on management of hepatitis C virus infection--2003.**
  Author(s): Hamid S, Umar M, Alam A, Siddiqui A, Qureshi H, Butt J; Pakistan Society of Gastroenterology.
  Source: J Pak Med Assoc. 2004 March; 54(3): 146-50. Review. No Abstract Available.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15129876

- **Qualitative detection of hepatitis C virus RNA: comparison of analytical sensitivity, clinical performance, and workflow of the Cobas Amplicor HCV test version 2.0 and the HCV RNA transcription-mediated amplification qualitative assay.**
  Author(s): Krajden M, Ziermann R, Khan A, Mak A, Leung K, Hendricks D, Comanor L.
  Source: Journal of Clinical Microbiology. 2002 August; 40(8): 2903-7.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12149349

- **Quantification and functional analysis of plasmacytoid dendritic cells in patients with chronic hepatitis C virus infection.**
  Author(s): Goutagny N, Vieux C, Decullier E, Ligeoix B, Epstein A, Trepo C, Couzigou P, Inchauspe G, Bain C.
  Source: The Journal of Infectious Diseases. 2004 May 1; 189(9): 1646-55. Epub 2004 April 15.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15116301

- **Quantification of hepatitis C virus (HCV) in liver specimens and sera from patients with human immunodeficiency virus coinfection by using the Versant HCV RNA 3.0 (branched DNA-based) DNA assay.**
  Author(s): Tedeschi R, Pivetta E, Zanussi S, Bidoli E, Ros M, di Gennaro G, Nasti G, De Paoli P.
  Source: Journal of Clinical Microbiology. 2003 July; 41(7): 3046-50.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12843041

- **Quantification of hepatitis C virus in human liver and serum samples by using LightCycler reverse transcriptase PCR.**
  Author(s): White PA, Pan Y, Freeman AJ, Marinos G, Ffrench RA, Lloyd AR, Rawlinson WD.
  Source: Journal of Clinical Microbiology. 2002 November; 40(11): 4346-8.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12409428

- **Quantitative assay of hepatitis C virus RNA using an automated extraction system for specific capture with probes and paramagnetic particle separation.**
  Author(s): Miyachi H, Masukawa A, Asai S, Miura T, Tamatsukuri S, Hirose T, Ando Y.
  Source: Journal of Clinical Microbiology. 2003 February; 41(2): 572-5.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12574248

- **Quantitative method of intracellular hepatitis C virus RNA using LightCycler PCR.**
  Author(s): Nozaki A, Kato N.
  Source: Acta Medica Okayama. 2002 April; 56(2): 107-10.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12002616

- **Quantitative signal of anti-HCV by an automated assay predicts viremia in a population at high prevalence of hepatitis C virus infection.**
  Author(s): Bossi V, Galli C.
  Source: Journal of Clinical Virology : the Official Publication of the Pan American Society for Clinical Virology. 2004 May; 30(1): 45-9.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15072753

- **Quasispecies heterogeneity and constraints on the evolution of the 5' noncoding region of hepatitis C virus (HCV): relationship with HCV resistance to interferon-alpha therapy.**
  Author(s): Soler M, Pellerin M, Malnou CE, Dhumeaux D, Kean KM, Pawlotsky JM.
  Source: Virology. 2002 June 20; 298(1): 160-73.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12093183

- **Rapid transmission of hepatitis C virus among young injecting heroin users in Southern China.**
  Author(s): Garten RJ, Lai S, Zhang J, Liu W, Chen J, Vlahov D, Yu XF.
  Source: International Journal of Epidemiology. 2004 February; 33(1): 182-8.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15075167

- **Reactive oxygen species suppress hepatitis C virus RNA replication in human hepatoma cells.**
  Author(s): Choi J, Lee KJ, Zheng Y, Yamaga AK, Lai MM, Ou JH.
  Source: Hepatology (Baltimore, Md.). 2004 January; 39(1): 81-9.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14752826

- **Relationship of oral lichen planus to hepatitis C virus in southern Taiwan.**
  Author(s): Chung CH, Yang YH, Chang TT, Shieh DB, Liu SY, Shieh TY.
  Source: Kaohsiung J Med Sci. 2004 April; 20(4): 151-9.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15191216

- **Response to "Hepatitis C virus, sickle cell disease treatment options"--a February letter to the editor.**
  Author(s): Smoot DT.
  Source: Journal of the National Medical Association. 2004 March; 96(3): 383.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15040523

- **Response to Soriano et al., 'Treatment of chronic hepatitis C virus infection: we must target the virus or liver fibrosis?'.**
  Author(s): Matthews G, Dore G.
  Source: Aids (London, England). 2003 December 5; 17(18): 2675-6.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14685063

- **Reverse transcriptase/polymerase chain reaction analyses of hemodialysis ultrafiltrates and sera of hepatitis C virus positive patients.**
  Author(s): Simjanovska LJ, Porcu K, Amitov V, Efremov GD, Polenakovic M.
  Source: Int J Artif Organs. 2004 January; 27(1): 35-9.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14984182

- **Ribavirin-associated hemoglobinuria with treatment of hepatitis C virus infection.**
  Author(s): Diamond C.
  Source: Clinical Infectious Diseases : an Official Publication of the Infectious Diseases Society of America. 2004 April 1; 38(7): 1042.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15034843

- **Risk of hepatitis C virus transmission following percutaneous exposure in healthcare workers.**
  Author(s): De Carli G, Puro V, Ippolito G; Studio Italiano Rischio Occupazionale da HIV Group.
  Source: Infection. 2003 December; 31 Suppl 2: 22-7.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15018469

- **Role of hepatitis C virus infection in malignant lymphoma in Spain.**
  Author(s): de Sanjose S, Nieters A, Goedert JJ, Domingo-Domenech E, Fernandez de Sevilla A, Bosch R, Herrera P, Domingo A, Petit J, Bosch X, Kallinowski B.
  Source: International Journal of Cancer. Journal International Du Cancer. 2004 August 10; 111(1): 81-5.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15185347

- **Role of replicative senescence in the progression of fibrosis in hepatitis C virus (HCV) recurrence after liver transplantation.**
  Author(s): Trak-Smayra V, Contreras J, Dondero F, Durand F, Dubois S, Sommacale D, Marcellin P, Belghiti J, Degott C, Paradis V.
  Source: Transplantation. 2004 June 15; 77(11): 1755-60.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15201678

- **Sensitivity of NS3 serine proteases from hepatitis C virus genotypes 2 and 3 to the inhibitor BILN 2061.**
  Author(s): Thibeault D, Bousquet C, Gingras R, Lagace L, Maurice R, White PW, Lamarre D.
  Source: Journal of Virology. 2004 July; 78(14): 7352-9.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15220408

- **Sequential changes of hepatitis C virus antibody profiles during treatment of chronic hepatitis C of genotype 1b: pretreatment antibody response to E2/NS1 correlated sustained response.**
  Author(s): Chu CM, Sheen IS, Liaw YF.
  Source: Infection. 2004 June; 32(3): 153-6.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15188075

- **Seroprevalence of hepatitis C virus infection among indigent urban pregnant women in Zimbabwe.**
  Author(s): Madzime S, William MA, Mohamed K, October T, Adem M, Mudzamiri S, Woelk GB.
  Source: Cent Afr J Med. 2000 January; 46(1): 1-4.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14674198

- **Seroprevalence of hepatitis C virus infection and its risk factors in pregnant women.**
  Author(s): Khokhar N, Raja KS, Javaid S.
  Source: J Pak Med Assoc. 2004 March; 54(3): 135. No Abstract Available.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15129873

- **Seroprevalence of human immunodeficiency virus, hepatitis B virus and hepatitis C virus among eye donors.**
  Author(s): Mahalakshmi B, Madhavan HN, Pushpalatha R, Margarita S.
  Source: Indian J Ophthalmol. 2004 March; 52(1): 61-2.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15132383

- **Serum immunoglobulins predict the extent of hepatic fibrosis in patients with chronic hepatitis C virus infection.**
  Author(s): Watt K, Uhanova J, Gong Y, Kaita K, Doucette K, Pettigrew N, Minuk GY.
  Source: Journal of Viral Hepatitis. 2004 May; 11(3): 251-6.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15117327

- **Specific inhibition of hepatitis C virus replication by cyclosporin A.**
  Author(s): Nakagawa M, Sakamoto N, Enomoto N, Tanabe Y, Kanazawa N, Koyama T, Kurosaki M, Maekawa S, Yamashiro T, Chen CH, Itsui Y, Kakinuma S, Watanabe M.
  Source: Biochemical and Biophysical Research Communications. 2004 January 2; 313(1): 42-7.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14672695

- **Splenic and nodal marginal zone lymphomas are indolent disorders at high hepatitis C virus seroprevalence with distinct presenting features but similar morphologic and phenotypic profiles.**
  Author(s): Arcaini L, Paulli M, Boveri E, Vallisa D, Bernuzzi P, Orlandi E, Incardona P, Brusamolino E, Passamonti F, Burcheri S, Schena C, Pascutto C, Cavanna L, Magrini U, Lazzarino M.
  Source: Cancer. 2004 January 1; 100(1): 107-15.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14692030

- **Steatosis and chronic hepatitis C virus infection.**
  Author(s): Khokhar N, Mushtaq M, Mukhtar AS, Ilahi F.
  Source: J Pak Med Assoc. 2004 March; 54(3): 110-2.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15129866

- **Sustained low alanine aminotransferase levels can predict the survival for 10 years without hepatocellular carcinoma development in patients with hepatitis C virus-associated liver cirrhosis of child stage A.**
  Author(s): Tarao K, Rino Y, Ohkawa S, Endo O, Miyakawa K, Tamai S, Hirokawa S, Masaki T, Nagaoka T, Okamoto N, Tanaka K, Tarao N.
  Source: Intervirology. 2004; 47(2): 65-71.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15192269

- **Targeting of hepatitis C virus core protein to mitochondria through a novel C-terminal localization motif.**
  Author(s): Schwer B, Ren S, Pietschmann T, Kartenbeck J, Kaehlcke K, Bartenschlager R, Yen TS, Ott M.
  Source: Journal of Virology. 2004 August; 78(15): 7958-68.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15254168

- **The -2518 promotor polymorphism in the MCP-1 gene is not associated with liver cirrhosis in chronic hepatitis C virus infection.**
  Author(s): Glas J, Torok HP, Tonenchi L, Schiemann U, Folwaczny C.
  Source: Gastroenterology. 2004 June; 126(7): 1930-1; Author Reply 1931-2.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15188212

- **The hypervariable region 1 of the E2 glycoprotein of hepatitis C virus binds to glycosaminoglycans, but this binding does not lead to infection in a pseudotype system.**
  Author(s): Basu A, Beyene A, Meyer K, Ray R.
  Source: Journal of Virology. 2004 May; 78(9): 4478-86.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15078928

- **The impact of nurse understaffing on the transmission of hepatitis C virus in a hospital-based hemodialysis unit.**
  Author(s): Saxena AK, Panhotra BR.
  Source: Medical Principles and Practice : International Journal of the Kuwait University, Health Science Centre. 2004 May-June; 13(3): 129-35.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15073424

- **The prevalence and the risk behaviours associated with the transmission of hepatitis C virus in Australian correctional facilities.**
  Author(s): Hellard ME, Hocking JS, Crofts N.
  Source: Epidemiology and Infection. 2004 June; 132(3): 409-15.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15188710

- **The prevalence of hepatitis C virus infection in patients with non-Hodgkin's lymphoma.**
  Author(s): Gisbert JP, Garcia-Buey L, Arranz R, Blas C, Pinilla I, Khorrami S, Acevedo A, Borque MJ, Pajares JM, Fernandez-Ranada JM, Moreno-Otero R.
  Source: European Journal of Gastroenterology & Hepatology. 2004 February; 16(2): 135-8.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15075985

- **The use of class-I HLA tetramers for the detection of hepatitis C virus NS3-specific CD8(+) T cells in patients with chronic infection.**
  Author(s): Lopez-Labrador FX, He XS, Berenguer M, Cheung RC, Wright TL, Greenberg HB.
  Source: Journal of Immunological Methods. 2004 April; 287(1-2): 91-9.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15099758

- **Transactivating effect of hepatitis C virus core protein: a suppression subtractive hybridization study.**
  Author(s): Liu M, Liu Y, Cheng J, Zhang SL, Wang L, Shao Q, Zhang J, Yang Q.
  Source: World Journal of Gastroenterology : Wjg. 2004 June 15; 10(12): 1746-9.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15188498

- **Treatment of chronic hepatitis C virus in the virginia department of corrections: can compliance overcome racial differences to response?**
  Author(s): Sterling RK, Hofmann CM, Luketic VA, Sanyal AJ, Contos MJ, Mills AS, Shiffman ML.
  Source: The American Journal of Gastroenterology. 2004 May; 99(5): 866-72.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15128352

- **Tumor necrosis factor-alpha-induced insulin resistance may mediate the hepatitis C virus-diabetes association.**
  Author(s): Knobler H, Zhornicky T, Sandler A, Haran N, Ashur Y, Schattner A.
  Source: The American Journal of Gastroenterology. 2003 December; 98(12): 2751-6.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14687828

- **Ultrastructural visualization of hepatitis C virus components in human and primate liver biopsies.**
  Author(s): De Vos R, Verslype C, Depla E, Fevery J, Van Damme B, Desmet V, Roskams T.
  Source: Journal of Hepatology. 2002 September; 37(3): 370-9.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12175633

- **Unexpected distribution of hepatitis C virus genotypes in patients on hemodialysis and kidney transplant recipients.**
  Author(s): Perez RM, Ferraz ML, Figueiredo MS, Contado D, Koide S, Ferreira AP, Cendoroglo Neto M, Medina Pestana JO, Silva AE.
  Source: Journal of Medical Virology. 2003 April; 69(4): 489-94.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12601756

- **Upregulation of endogenous intrahepatic interferon stimulated genes during chronic hepatitis C virus infection.**
  Author(s): MacQuillan GC, Mamotte C, Reed WD, Jeffrey GP, Allan JE.
  Source: Journal of Medical Virology. 2003 June; 70(2): 219-27.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12696108

- **Upregulation of major histocompatibility complex class I on liver cells by hepatitis C virus core protein via p53 and TAP1 impairs natural killer cell cytotoxicity.**
  Author(s): Herzer K, Falk CS, Encke J, Eichhorst ST, Ulsenheimer A, Seliger B, Krammer PH.
  Source: Journal of Virology. 2003 August; 77(15): 8299-309.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12857899

- **Use and interpretation of hepatitis C virus diagnostic assays.**
  Author(s): Pawlotsky JM.
  Source: Clinics in Liver Disease. 2003 February; 7(1): 127-37. Review.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12691462

- **Use of fluoroquinolones in patients with chronic hepatitis C virus-induced liver failure.**
  Author(s): Kojima H, Kaita KD, Hawkins K, Uhanova J, Minuk GY.
  Source: Antimicrobial Agents and Chemotherapy. 2002 October; 46(10): 3280-2.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12234860

- **Use of phylogenetic analysis of hepatitis C virus (HCV) hypervariable region 1 sequences to trace an outbreak of HCV in an autodialysis unit.**
  Author(s): Halfon P, Roubicek C, Gerolami V, Quentin Y, Khiri H, Pepe G, Berland Y.
  Source: Journal of Clinical Microbiology. 2002 April; 40(4): 1541-5.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=11923392

- **Use of polymerase chain reaction for early detection and management of hepatitis C virus infection after needlestick injury.**
  Author(s): Wang TY, Kuo HT, Chen LC, Chen YT, Lin CN, Lee MM.
  Source: Ann Clin Lab Sci. 2002 Spring; 32(2): 137-41.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12017194

- **Use of versant TMA and bDNA 3.0 assays to detect and quantify hepatitis C virus in semen.**
  Author(s): Pekler VA, Robbins WA, Nyamathi A, Yashina TL, Leak B, Robins TA.
  Source: Journal of Clinical Laboratory Analysis. 2003; 17(6): 264-70.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14614751

- **Uselessness of liver biopsy in patients with hepatitis C virus chronic infection and persistently normal aminotransferase levels.**
  Author(s): Pasquale G, Sagnelli E, Coppola N, Scarano F, Scolastico C, Sagnelli C, Bellomo PF, Lettieri A, Filippini P, Piccinino F.
  Source: Infez Med. 2003 March; 11(1): 11-7.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12719665

- **Values of high-resolution computed tomography and pulmonary function tests in managements of patients with chronic hepatitis C virus infection.**
  Author(s): Okutan O, Kartaloglu Z, Ilvan A, Kutlu A, Bozkanat E, Silit E.
  Source: World Journal of Gastroenterology : Wjg. 2004 February 1; 10(3): 381-4.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14760762

- **Variation of hepatitis C virus load, hypervariable region 1 quasispecies and CD81 hepatocyte expression in hepatocellular carcinoma and adjacent non-cancerous liver.**
  Author(s): Young KC, Lin PW, Hsiao WC, Chang TT, Chang YC, Wu HL.
  Source: Journal of Medical Virology. 2002 October; 68(2): 188-96.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12210407

- **Vertical transmission of the hepatitis C virus to infants of anti-human immunodeficiency virus-negative mothers: molecular evolution of hypervariable region 1 in prenatal and perinatal or postnatal infections.**
  Author(s): Caudai C, Battiata M, Riccardi MP, Toti M, Bonazza P, Padula MG, Pianese M, Valensin PE.
  Source: Journal of Clinical Microbiology. 2003 August; 41(8): 3955-9.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12904428

- **Very rapid evolution of infection with hepatitis C virus transmitted by an accidental needlestick.**
  Author(s): Garcia JM, Serrano PL, Terron Sdel C, Marugan RB, Garcia GM, Grande LG, Miquel J, Plaza AG.
  Source: Clinical Infectious Diseases : an Official Publication of the Infectious Diseases Society of America. 2003 June 15; 36(12): 1632-4.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12802777

- **Viral clearance occurs very early during the natural resolution of hepatitis C virus infection in persons with haemophilia.**
  Author(s): Eyster ME, Sanders J, Goedert JJ.
  Source: Haemophilia : the Official Journal of the World Federation of Hemophilia. 2004 January; 10(1): 75-80.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14962224

- **Viral etiopathogenesis of Sjogren's syndrome: role of the hepatitis C virus.**
  Author(s): Ramos-Casals M, Garcia-Carrasco M, Brito Zeron MP, Cervera R, Font J.
  Source: Autoimmunity Reviews. 2002 August; 1(4): 238-43. Review.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12849002

- **Viral kinetics in hepatitis C virus: special patient populations.**
  Author(s): Layden-Almer JE, Layden TJ.
  Source: Seminars in Liver Disease. 2003; 23 Suppl 1: 29-33. Review.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12934166

- **Virological significance of low-level hepatitis B virus infection in patients with hepatitis C virus associated liver disease.**
  Author(s): Tanaka T, Inoue K, Hayashi Y, Abe A, Tsukiyama-Kohara K, Nuriya H, Aoki Y, Kawaguchi R, Kubota K, Yoshiba M, Koike M, Tanaka S, Kohara M.
  Source: Journal of Medical Virology. 2004 February; 72(2): 223-9.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14695663

- **Virus-host cell interactions during hepatitis C virus RNA replication: impact of polyprotein expression on the cellular transcriptome and cell cycle association with viral RNA synthesis.**
  Author(s): Scholle F, Li K, Bodola F, Ikeda M, Luxon BA, Lemon SM.
  Source: Journal of Virology. 2004 February; 78(3): 1513-24.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14722306

- **Virus-specific effector CD4+ T-cell responses in hemodialysis patients with hepatitis C virus infection.**
  Author(s): Rico MA, Ruiz S, Subira D, Barril G, Cigarran S, Castanon S, Quiroga JA, Selgas R, Carreno V.
  Source: Journal of Medical Virology. 2004 January; 72(1): 66-74.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14635013

- **Whole stimulated salivary flow in patients with chronic hepatitis C virus infection.**
  Author(s): Ferreiro MC, Prieto MH, Rodriguez SB, Vazquez RL, Iglesias AC, Dios PD.
  Source: Journal of Oral Pathology & Medicine : Official Publication of the International Association of Oral Pathologists and the American Academy of Oral Pathology. 2002 February; 31(2): 117-20. Review.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=11896834

CHAPTER 2. NUTRITION AND HEPATITIS C VIRUS

Overview

In this chapter, we will show you how to find studies dedicated specifically to nutrition and hepatitis C virus.

Finding Nutrition Studies on Hepatitis C Virus

The National Institutes of Health's Office of Dietary Supplements (ODS) offers a searchable bibliographic database called the IBIDS (International Bibliographic Information on Dietary Supplements; National Institutes of Health, Building 31, Room 1B29, 31 Center Drive, MSC 2086, Bethesda, Maryland 20892-2086, Tel: 301-435-2920, Fax: 301-480-1845, E-mail: ods@nih.gov). The IBIDS contains over 460,000 scientific citations and summaries about dietary supplements and nutrition as well as references to published international, scientific literature on dietary supplements such as vitamins, minerals, and botanicals.[7] The IBIDS includes references and citations to both human and animal research studies.

As a service of the ODS, access to the IBIDS database is available free of charge at the following Web address: **http://ods.od.nih.gov/databases/ibids.html**. After entering the search area, you have three choices: (1) IBIDS Consumer Database, (2) Full IBIDS Database, or (3) Peer Reviewed Citations Only.

Now that you have selected a database, click on the "Advanced" tab. An advanced search allows you to retrieve up to 100 fully explained references in a comprehensive format. Type "hepatitis C virus" (or synonyms) into the search box, and click "Go." To narrow the search, you can also select the "Title" field.

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[7] Adapted from **http://ods.od.nih.gov**. IBIDS is produced by the Office of Dietary Supplements (ODS) at the National Institutes of Health to assist the public, healthcare providers, educators, and researchers in locating credible, scientific information on dietary supplements. IBIDS was developed and will be maintained through an interagency partnership with the Food and Nutrition Information Center of the National Agricultural Library, U.S. Department of Agriculture.

The following information is typical of that found when using the "Full IBIDS Database" to search for "hepatitis C virus" (or a synonym):

- **A nested case-control study on association between hepatitis C virus antibodies and primary liver cancer in a cohort of 9,775 men in Taiwan.**
  Author(s): Institute of Public Health, National Taiwan University College of Public Health, Taipei.
  Source: Chang, C C Yu, M W Lu, C F Yang, C S Chen, C J J-Med-Virol. 1994 July; 43(3): 276-80 0146-6615

- **A reliable internally controlled RT-nested PCR method for the detection of hepatitis C virus RNA.**
  Author(s): Department of Molecular Biology, Institute of Cellular and Molecular Biology, Okayama University Medical School, Japan.
  Source: Nozaki, A Naganuma, A Nakamura, T Tanaka, K Sekihara, H Kato, N Acta-Med-Okayama. 2000 December; 54(6): 253-7 0386-300X

- **A synthetic peptide derived from the non-structural protein 3 of hepatitis C virus serves as a specific substrate for PKC.**
  Author(s): Bernhard-Nocht-Institut fur Tropenmedizin, Hamburg, Germany.
  Source: Borowski, P Resch, K Schmitz, H Heiland, M Biol-Chem. 2000 January; 381(1): 19-27 1431-6730

- **Characterization and mutational analysis of the helicase and NTPase activities of hepatitis C virus full-length NS3 protein.**
  Author(s): Department of Medicine, Imperial College School of Medicine, London, UK.
  Source: Wardell, A D Errington, W Ciaramella, G Merson, J McGarvey, M J J-Gen-Virol. 1999 March; 80 (Pt 3)701-9 0022-1317

- **Characterization of antiviral activity of lactoferrin against hepatitis C virus infection in human cultured cells.**
  Author(s): Virology and Glycobiology Division, National Cancer Center Research Institute, 5-1-1, Tsukiji, Chuo-ku, Tokyo, Japan.
  Source: Ikeda, M Nozaki, A Sugiyama, K Tanaka, T Naganuma, A Tanaka, K Sekihara, H Shimotohno, K Saito, M Kato, N Virus-Res. 2000 January; 66(1): 51-63 0168-1702

- **Direct in situ reverse transcriptase-linked polymerase chain reaction with biotinylated primers for the detection of hepatitis C virus RNA in liver biopsies.**
  Author(s): Laboratoire de Virologie-Biologie Cellulaire, Institut d'Etude et de Transfert de Genes, Faculte Mixte de Medecine et de Pharmacie, Besancon, France.
  Source: Bettinger, D Mougin, C Fouque, B Kantelip, B Miguet, J P Lab, M J-Clin-Virol. 1999 May; 12(3): 233-41 1386-6532

- **DNA helicase activity of the hepatitis C virus nonstructural protein 3.**
  Author(s): Department of Biological Sciences, Korea Advanced Institute of Science and Technology, Taejon.
  Source: Gwack, Y Kim, D W Han, J H Choe, J Eur-J-Biochem. 1997 November 15; 250(1): 47-54 0014-2956

- **Ectopic expression of hepatitis C virus core protein differentially regulates nuclear transcription factors.**
  Author(s): Cytokine Research Laboratory, Department of Molecular Oncology, The University of Texas M. D. Anderson Cancer Center, Houston, Texas 77030, USA.
  Source: Shrivastava, A Manna, S K Ray, R Aggarwal, B B J-Virol. 1998 December; 72(12): 9722-8 0022-538X

- **Effect of phenolic and chlorine disinfectants on hepatitis C virus binding and infectivity.**
  Author(s): Department of Biomedical Sciences, University of Trieste, Italy.
  Source: Agolini, G Russo, A Clementi, M Am-J-Infect-Control. 1999 June; 27(3): 236-9 0196-6553

- **Fulminant hepatitis caused by hepatitis C virus during treatment for multiple sclerosis.**
  Author(s): First Department of Internal Medicine, Akita University School of Medicine, Japan.
  Source: Funaoka, M Kato, K Komatsu, M Ono, T Hoshino, T Kato, J Kuramitsu, T Ishii, T Toyoshima, I Masamune, O J-Gastroenterol. 1996 February; 31(1): 119-22 0944-1174

- **Inhibition of hepatitis C virus adsorption to peripheral blood mononuclear cells by dextran sulfate.**
  Author(s): INSERM U74, Strasbourg, France.
  Source: Cribier, B Schmitt, C Kirn, A Stoll Keller, F Arch-Virol. 1998; 143(2): 375-9 0304-8608

- **Interferon therapy in hepatitis C virus (HCV) induced chronic hepatitis: clinical significance of pretreatment with glycyrhizine.**
  Author(s): Department of Internal Medicine, Jikei University School of Medicine, Japan.
  Source: Fujisawa, K Trop-Gastroenterol. 1991 Oct-December; 12(4): 176-9 0250-636X

- **Lactoferrin inhibits hepatitis C virus viremia in patients with chronic hepatitis C: a pilot study.**
  Author(s): Third Department of Internal Medicine, Yokohama City University School of Medicine, Yokohama. tanaka97@med.yokohama-cu.ac.jp
  Source: Tanaka, K Ikeda, M Nozaki, A Kato, N Tsuda, H Saito, S Sekihara, H Jpn-J-Cancer-Res. 1999 April; 90(4): 367-71 0910-5050

- **Mechanism of de novo initiation by the hepatitis C virus RNA-dependent RNA polymerase: role of divalent metals.**
  Author(s): Department of Biology, Indiana University, 1001 E. Third Street, Bloomington, IN 47405, USA.
  Source: Ranjith KuMarch, C T Kim, Y C Gutshall, L Silverman, C Khandekar, S Sarisky, R T Kao, C C J-Virol. 2002 December; 76(24): 12513-25 0022-538X

- **Medicinal herbs for hepatitis C virus infection (Cochrane Review).**
  Author(s): The Cochrane Hepato-Biliary Group, Copenhagen Trial Unit, Centre for Clinical Intervention Research, Copenhagen University Hospital, Dept. 7701, H:S Rigshospitalet, Blegdamsvej 9, Copenhagen, DENMARK, DK-2100. Jianping l@hotmail.com
  Source: Liu, J P Manheimer, E Tsutani, K Gluud, C Cochrane-Database-Syst-Revolume 2001; 4: CD003183 1469-493X

- **Phosphorylation of the hepatitis C virus NS5A protein in vitro and in vivo: properties of the NS5A-associated kinase.**
  Author(s): Department of Molecular Microbiology, Washington University School of Medicine, St. Louis, Missouri 63110-1093, USA.
  Source: Reed, K E Xu, J Rice, C M J-Virol. 1997 October; 71(10): 7187-97 0022-538X

- **Reconstitution of hepatitis C virus protease activities in yeast.**
  Author(s): Molecular Biology and Virology Section, Wyeth-Ayerst Research, 401 N. Middletown Road, Pearl River, NY 10965, USA. makp@war.wyeth.com

Source: Mak, P Palant, O Labonte, P Plotch, S FEBS-Lett. 2001 August 10; 503(1): 13-8 0014-5793

- **Relationship between infection with hepatitis C virus and hepatocellular carcinoma in Japan.**
  Author(s): Department of Medicine, St Marianna University School of Medicine, Kanagawa, Japan.
  Source: Iino, S Antivir-Ther. 1998; 3(Suppl 3): 143-6 1359-6535
- **Role of the asialoglycoprotein receptor in binding and entry of hepatitis C virus structural proteins in cultured human hepatocytes.**
  Author(s): Edison Biotechnology Institute and College of Osteopathic Medicine, Ohio University, Athens 45701, USA. saunier@ohiou.edu
  Source: Saunier, B Triyatni, M Ulianich, L Maruvada, P Yen, P Kohn, L D J-Virol. 2003 January; 77(1): 546-59 0022-538X
- **The hepatitis C virus internal ribosome entry site adopts an ion-dependent tertiary fold.**
  Author(s): Department of Molecular Biophysics and Biochemistry and Howard Hughes Medical Institute, Yale University, New Haven, CT 06520-8114, USA.
  Source: Kieft, J S Zhou, K Jubin, R Murray, M G Lau, J Y Doudna, J A J-Mol-Biol. 1999 September 24; 292(3): 513-29 0022-2836
- **Treatment strategies for chronic hepatitis C virus infection.**
  Author(s): Department of General Medicine, Osaka University Hospital, Suita, Japan.
  Source: Kasahara, A J-Gastroenterol. 2000; 35(6): 411-23 0944-1174

Federal Resources on Nutrition

In addition to the IBIDS, the United States Department of Health and Human Services (HHS) and the United States Department of Agriculture (USDA) provide many sources of information on general nutrition and health. Recommended resources include:

- healthfinder®, HHS's gateway to health information, including diet and nutrition: **http://www.healthfinder.gov/scripts/SearchContext.asp?topic=238&page=0**
- The United States Department of Agriculture's Web site dedicated to nutrition information: **www.nutrition.gov**
- The Food and Drug Administration's Web site for federal food safety information: **www.foodsafety.gov**
- The National Action Plan on Overweight and Obesity sponsored by the United States Surgeon General: **http://www.surgeongeneral.gov/topics/obesity/**
- The Center for Food Safety and Applied Nutrition has an Internet site sponsored by the Food and Drug Administration and the Department of Health and Human Services: **http://vm.cfsan.fda.gov/**
- Center for Nutrition Policy and Promotion sponsored by the United States Department of Agriculture: **http://www.usda.gov/cnpp/**
- Food and Nutrition Information Center, National Agricultural Library sponsored by the United States Department of Agriculture: **http://www.nal.usda.gov/fnic/**
- Food and Nutrition Service sponsored by the United States Department of Agriculture: **http://www.fns.usda.gov/fns/**

Additional Web Resources

A number of additional Web sites offer encyclopedic information covering food and nutrition. The following is a representative sample:

- AOL: **http://search.aol.com/cat.adp?id=174&layer=&from=subcats**
- Family Village: **http://www.familyvillage.wisc.edu/med_nutrition.html**
- Google: **http://directory.google.com/Top/Health/Nutrition/**
- Healthnotes: **http://www.healthnotes.com/**
- Open Directory Project: **http://dmoz.org/Health/Nutrition/**
- Yahoo.com: **http://dir.yahoo.com/Health/Nutrition/**
- WebMD®Health: **http://my.webmd.com/nutrition**
- WholeHealthMD.com: **http://www.wholehealthmd.com/reflib/0,1529,00.html**

CHAPTER 3. ALTERNATIVE MEDICINE AND HEPATITIS C VIRUS

Overview

In this chapter, we will begin by introducing you to official information sources on complementary and alternative medicine (CAM) relating to hepatitis C virus. At the conclusion of this chapter, we will provide additional sources.

National Center for Complementary and Alternative Medicine

The National Center for Complementary and Alternative Medicine (NCCAM) of the National Institutes of Health (**http://nccam.nih.gov/**) has created a link to the National Library of Medicine's databases to facilitate research for articles that specifically relate to hepatitis C virus and complementary medicine. To search the database, go to the following Web site: **http://www.nlm.nih.gov/nccam/camonpubmed.html**. Select "CAM on PubMed." Enter "hepatitis C virus" (or synonyms) into the search box. Click "Go." The following references provide information on particular aspects of complementary and alternative medicine that are related to hepatitis C virus:

- **A case-control study of risk factors for sporadic hepatitis C virus infection in the southwestern United States.**
  Author(s): Balasekaran R, Bulterys M, Jamal MM, Quinn PG, Johnston DE, Skipper B, Chaturvedi S, Arora S.
  Source: The American Journal of Gastroenterology. 1999 May; 94(5): 1341-6.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=10235216

- **A case-control study on the risk factors of hepatitis C virus infection among Koreans.**
  Author(s): Kim YS, Ahn YO, Kim DW.
  Source: Journal of Korean Medical Science. 1996 February; 11(1): 38-43.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=8703369

- **A survey of antibodies to hepatitis C virus in Ethiopia.**
  Author(s): Frommel D, Tekle-Haimanot R, Berhe N, Aussel L, Verdier M, Preux PM, Denis F.
  Source: The American Journal of Tropical Medicine and Hygiene. 1993 October; 49(4): 435-9.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=7692753

- **An in vitro system combined with an in-house quantitation assay for screening hepatitis C virus inhibitors.**
  Author(s): Ho TY, Wu SL, Lai IL, Cheng KS, Kao ST, Hsiang CY.
  Source: Antiviral Research. 2003 May; 58(3): 199-208.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12767467

- **Analyzing the mechanisms of interferon-induced apoptosis using CrmA and hepatitis C virus NS5A.**
  Author(s): Ezelle HJ, Balachandran S, Sicheri F, Polyak SJ, Barber GN.
  Source: Virology. 2001 March 1; 281(1): 124-37.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=11222103

- **Approach to the patient with chronic hepatitis C virus infection.**
  Author(s): Herrine SK.
  Source: Annals of Internal Medicine. 2002 May 21; 136(10): 747-57.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12020143

- **Cleavage activity of hepatitis C virus serine proteinase.**
  Author(s): Kakiuchi N, Komoda Y, Hijikata M, Shimotohno K.
  Source: Journal of Biochemistry. 1997 October; 122(4): 749-55.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=9399578

- **Combination therapy with interferon alpha and ribavirin for chronic hepatitis C virus infection in thalassaemic patients.**
  Author(s): Telfer PT, Garson JA, Whitby K, Grant PR, Yardumian A, Hoffbrand AV, Wonke B.
  Source: British Journal of Haematology. 1997 September; 98(4): 850-5.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=9326177

- **Effects of handling and storage of blood on the stability of hepatitis C virus RNA: implications for NAT testing in transfusion practice.**
  Author(s): Grant PR, Kitchen A, Barbara JA, Hewitt P, Sims CM, Garson JA, Tedder RS.
  Source: Vox Sanguinis. 2000; 78(3): 137-42.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=10838513

- **Effects of iron loading on pathogenicity in hepatitis C virus-infected chimpanzees.**
  Author(s): Bassett SE, Di Bisceglie AM, Bacon BR, Sharp RM, Govindarajan S, Hubbard GB, Brasky KM, Lanford RE.
  Source: Hepatology (Baltimore, Md.). 1999 June; 29(6): 1884-92.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=10347134

- **Effects of storage and type of blood collection tubes on hepatitis C virus level in whole blood samples.**
  Author(s): Kessler HH, Stelzl E, Raggam RB, Haas J, Kirchmeir F, Hegenbarth K, Daghofer E, Santner BI, Marth E, Stauber RE.
  Source: Journal of Clinical Microbiology. 2001 May; 39(5): 1788-90.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=11325991

- **Epidemiology of hepatitis C virus infection in chronic haemodialysis.**
  Author(s): Chauveau P.
  Source: Nephrology, Dialysis, Transplantation : Official Publication of the European Dialysis and Transplant Association - European Renal Association. 1996; 11 Suppl 4: 39-41. Review.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=8918751

- **Establishment of a simple assay in vitro for hepatitis C virus NS3 serine protease based on recombinant substrate and single-chain protease.**
  Author(s): Du GX, Hou LH, Guan RB, Tong YG, Wang HT.
  Source: World Journal of Gastroenterology : Wjg. 2002 December; 8(6): 1088-93.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12439931

- **Fully automated detection of hepatitis C virus RNA in serum and whole-blood samples.**
  Author(s): Kessler HH, Clarici AM, Stelzl E, Muhlbauer G, Daghofer E, Santner BI, Marth E, Stauber RE.
  Source: Clinical and Diagnostic Laboratory Immunology. 2002 November; 9(6): 1385-8.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12414781

- **Genetic heterogeneity of the hepatitis C virus.**
  Author(s): Bukh J, Miller RH, Purcell RH.
  Source: Princess Takamatsu Symp. 1995; 25: 75-91. Review.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=8875612

- **Hepatitis C virus (HCV)-induced IgG-IgM rheumatoid factor (RF) complex may be the main causal factor for cold-dependent activation of complement in patients with rheumatic disease.**
  Author(s): Wei G, Yano S, Kuroiwa T, Hiromura K, Maezawa A.

Source: Clinical and Experimental Immunology. 1997 January; 107(1): 83-8.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=9010261

- **Hepatitis C virus acute exacerbation during chemotherapy and radiotherapy for oesophageal carcinoma.**
Author(s): de Pree C, Giostra E, Galetto A, Perrin L, Zulian GB.
Source: Annals of Oncology : Official Journal of the European Society for Medical Oncology / Esmo. 1994 November; 5(9): 861-2.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=7848891

- **Hepatitis C virus infection and liver disease in children with thalassemia.**
Author(s): Locasciulli A, Monguzzi W, Tornotti G, Bianco P, Masera G.
Source: Bone Marrow Transplantation. 1993; 12 Suppl 1: 18-20.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=7690633

- **Hepatitis c virus infection in employees of a large university hospital in Israel.**
Author(s): Sermoneta-Gertel S, Donchin M, Adler R, Baras M, Perlstein T, Manny N, Shouval D, Galun E.
Source: Infection Control and Hospital Epidemiology : the Official Journal of the Society of Hospital Epidemiologists of America. 2001 December; 22(12): 754-61.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=11876453

- **Hepatitis C virus infection in the United States.**
Author(s): Alter MJ.
Source: Journal of Hepatology. 1999; 31 Suppl 1: 88-91. Review.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=10622567

- **Hepatitis C virus.**
Author(s): Jarrett M, Cox P.
Source: Nurs Clin North Am. 2004 March; 39(1): 219-29. Review.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15062738

- **Hepatitis C virus-induced leuko-thrombocytopenia and haemolysis.**
Author(s): Emilia G, Luppi M, Ferrari MG, Barozzi P, Marasca R, Torelli G.
Source: Journal of Medical Virology. 1997 October; 53(2): 182-4.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=9334931

- **Hepatitis C virus-polymerase chain reaction minipool testing: 3 years in the largest Swiss blood transfusion service.**
Author(s): Stolz M, Gilgen M, Niederhauser C.

Source: Vox Sanguinis. 2003 February; 84(2): 105-10.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12609016

- **Hepatocellular carcinoma associated with hepatitis C virus infection in Japan: projection to other countries in the foreseeable future.**
  Author(s): Yoshizawa H.
  Source: Oncology. 2002; 62 Suppl 1: 8-17.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=11868791

- **Herbal and complementary and alternative medicine therapies for liver disease. A focus on Chinese traditional medicine in hepatitis C virus.**
  Author(s): Cohen MR.
  Source: Clinics in Liver Disease. 2001 May; 5(2): 461-78, Vii. Review.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=11385972

- **In vitro cold activation of complement shown by an overestimation of total complement 4: a study in patients with hepatitis C virus infection.**
  Author(s): Maguire OC, Curry MP, O'Gorman P, Parfrey N, Hegarty J, Cunningham SK.
  Source: Annals of Clinical Biochemistry. 2001 November; 38(Pt 6): 687-93.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=11732652

- **In vitro study of the NS2-3 protease of hepatitis C virus.**
  Author(s): Pieroni L, Santolini E, Fipaldini C, Pacini L, Migliaccio G, La Monica N.
  Source: Journal of Virology. 1997 September; 71(9): 6373-80.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=9261354

- **Inhibitory effects of sudanese medicinal plant extracts on hepatitis C virus (HCV) protease.**
  Author(s): Hussein G, Miyashiro H, Nakamura N, Hattori M, Kakiuchi N, Shimotohno K.
  Source: Phytotherapy Research : Ptr. 2000 November; 14(7): 510-6.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=11054840

- **Injection with nondisposable needles as an important route for transmission of acute community-acquired hepatitis C virus infection in Taiwan.**
  Author(s): Chen TZ, Wu JC, Yen FS, Sheng WY, Hwang SJ, Huo TI, Lee SD.
  Source: Journal of Medical Virology. 1995 July; 46(3): 247-51.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=7561798

- **Intrafamilial transmission of hepatitis C virus in hemodialysis patients.**
  Author(s): Hou CH, Chen WY, Kao JH, Chen DS, Yang Y, Chen JJ, Lee SH, Wu DJ, Yang SC.

Source: Journal of Medical Virology. 1995 April; 45(4): 381-5.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=7545208

- **Intrahepatic cytokine profiles associated with posttransplantation hepatitis C virus-related liver injury.**
  Author(s): Zekry A, Bishop GA, Bowen DG, Gleeson MM, Guney S, Painter DM, McCaughan GW.
  Source: Liver Transplantation : Official Publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society. 2002 March; 8(3): 292-301.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=11910576

- **Intraspousal transmission of GB virus C/hepatitis G virus in an hepatitis C virus hyperendemic area in Japan.**
  Author(s): Akiyoshi F, Sata M, Noguchi S, Suzuki H, Ide T, Uchimura Y, Sasaki M, Tanaka K, Miyajima I, Mizokami M, Tanikawa K.
  Source: The American Journal of Gastroenterology. 1999 June; 94(6): 1627-31.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=10364035

- **Low prevalence of hepatitis C virus infection among hospital staff and acupuncturists in Kyushu, Japan.**
  Author(s): Nakashima K, Kashiwagi S, Hayashi J, Noguchi A, Hirata M, Ikeda S, Sakota I, Shingu T.
  Source: The Journal of Infection. 1993 January; 26(1): 17-25.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=7681088

- **Lower erythropoietin and iron supplementation are required in hemodialysis patients with hepatitis C virus infection.**
  Author(s): Altintepe L, Kurtoglu E, Tonbul Z, Yeksan M, Yildiz A, Turk S.
  Source: Clinical Nephrology. 2004 May; 61(5): 347-51.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15182130

- **Medicinal herbs for hepatitis C virus infection.**
  Author(s): Liu JP, Manheimer E, Tsutani K, Gluud C.
  Source: Cochrane Database Syst Rev. 2001; (4): Cd003183. Review.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=11687177

- **Medicinal herbs for hepatitis C virus infection: a Cochrane hepatobiliary systematic review of randomized trials.**
  Author(s): Liu J, Manheimer E, Tsutani K, Gluud C.
  Source: The American Journal of Gastroenterology. 2003 March; 98(3): 538-44. Review.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12650784

- **Mitral valve vegetation and cerebral emboli in a primary antiphospholipid syndrome patient who had hepatitis C virus infection: report of a case and review of the literature.**
  Author(s): Pamuk ON, Cakir N, Soy M, Aktoz M, Celik Y, Akdemir O.
  Source: Clinical Rheumatology. 2003 May; 22(2): 136-9. Review.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12740679

- **Molecular analysis of intraspousal transmission of hepatitis C virus.**
  Author(s): Chayama K, Kobayashi M, Tsubota A, Koida I, Arase Y, Saitoh S, Ikeda K, Kumada H.
  Source: Journal of Hepatology. 1995 April; 22(4): 431-9.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=7665861

- **Pharmacokinetics, safety, and antiviral effects of hypericin, a derivative of St. John's wort plant, in patients with chronic hepatitis C virus infection.**
  Author(s): Jacobson JM, Feinman L, Liebes L, Ostrow N, Koslowski V, Tobia A, Cabana BE, Lee D, Spritzler J, Prince AM.
  Source: Antimicrobial Agents and Chemotherapy. 2001 February; 45(2): 517-24.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=11158749

- **Plastic microchip electrophoresis for analysis of PCR products of hepatitis C virus.**
  Author(s): Chen YH, Wang WC, Young KC, Chang TT, Chen SH.
  Source: Clinical Chemistry. 1999 November; 45(11): 1938-43.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=10545063

- **Prevalence and risk factors of hepatitis C virus infection among Koreans in rural area of Korea.**
  Author(s): Shin HR, Kim JY, Ohno T, Cao K, Mizokami M, Risch H, Kim SR.
  Source: Hepatology Research : the Official Journal of the Japan Society of Hepatology. 2000 June; 17(3): 185-196.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=10794972

- **Prevalence of anti-hepatitis C virus antibody and chronic liver disease among atomic bomb survivors.**
  Author(s): Fujiwara S, Kusumi S, Cologne J, Akahoshi M, Kodama K, Yoshizawa H.
  Source: Radiation Research. 2000 July; 154(1): 12-9.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=10856960

- **Prevalence, infectivity, and risk factor analysis of hepatitis C virus infection in prostitutes.**
  Author(s): Wu JC, Lin HC, Jeng FS, Ma GY, Lee SD, Sheng WY.

Source: Journal of Medical Virology. 1993 April; 39(4): 312-7.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=8492103

- **Prospective multicenter clinical evaluation of AMPLICOR and COBAS AMPLICOR hepatitis C virus tests.**
Author(s): Nolte FS, Fried MW, Shiffman ML, Ferreira-Gonzalez A, Garrett CT, Schiff ER, Polyak SJ, Gretch DR.
Source: Journal of Clinical Microbiology. 2001 November; 39(11): 4005-12.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=11682522

- **Risk factors for hepatitis C virus infection. A case-control study of blood donors in the Trent Region (UK).**
Author(s): Neal KR, Jones DA, Killey D, James V.
Source: Epidemiology and Infection. 1994 June; 112(3): 595-601.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=8005225

- **Simultaneous extraction of hepatitis C virus (HCV), hepatitis B virus, and HIV-1 from plasma and detection of HCV RNA by a reverse transcriptase-polymerase chain reaction assay designed for screening pooled units of donated blood.**
Author(s): Sun R, Schilling W, Jayakar H, Ku J, Wang J, Rosenstraus M, Spadoro J.
Source: Transfusion. 1999 October; 39(10): 1111-9.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=10532606

- **Stability of hepatitis C virus RNA during specimen handling and storage prior to NASBA amplification.**
Author(s): Damen M, Sillekens P, Sjerps M, Melsert R, Frantzen I, Reesink HW, Lelie PN, Cuypers HT.
Source: Journal of Virological Methods. 1998 June; 72(2): 175-84.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=9694325

- **Storage conditions of blood samples and primer selection affect the yield of cDNA polymerase chain reaction products of hepatitis C virus.**
Author(s): Cuypers HT, Bresters D, Winkel IN, Reesink HW, Weiner AJ, Houghton M, van der Poel CL, Lelie PN.
Source: Journal of Clinical Microbiology. 1992 December; 30(12): 3220-4.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=1333489

- **The hepatitis C virus internal ribosome entry site adopts an ion-dependent tertiary fold.**
Author(s): Kieft JS, Zhou K, Jubin R, Murray MG, Lau JY, Doudna JA.
Source: Journal of Molecular Biology. 1999 September 24; 292(3): 513-29.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=10497018

- **The N-terminal region of NS3 serine proteinase of hepatitis C virus is important to maintain its enzymatic integrity.**
  Author(s): Mori A, Yuasa S, Yamada K, Nagami Y, Miyamura T.
  Source: Biochemical and Biophysical Research Communications. 1997 February 24; 231(3): 738-42.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=9070884

- **Transmission of hepatitis C virus in Asia: past and present perspectives.**
  Author(s): Kao JH, Chen DS.
  Source: Journal of Gastroenterology and Hepatology. 2000 May; 15 Suppl: E91-6. Review.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=10921389

- **Transmission of hepatitis C virus in Taiwan: prevalence and risk factors based on a nationwide survey.**
  Author(s): Sun CA, Chen HC, Lu CF, You SL, Mau YC, Ho MS, Lin SH, Chen CJ.
  Source: Journal of Medical Virology. 1999 November; 59(3): 290-6.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=10502258

- **Treatment of chronic hepatitis C virus infection.**
  Author(s): Malnick SD, Beergabel M, Lurie Y.
  Source: The Annals of Pharmacotherapy. 2000 October; 34(10): 1156-64. Review.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=11054985

- **Treatment strategies for chronic hepatitis C virus infection.**
  Author(s): Kasahara A.
  Source: Journal of Gastroenterology. 2000; 35(6): 411-23. Review.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=10864347

Additional Web Resources

A number of additional Web sites offer encyclopedic information covering CAM and related topics. The following is a representative sample:

- Alternative Medicine Foundation, Inc.: **http://www.herbmed.org/**
- AOL: **http://search.aol.com/cat.adp?id=169&layer=&from=subcats**
- Chinese Medicine: **http://www.newcenturynutrition.com/**
- drkoop.com®: **http://www.drkoop.com/InteractiveMedicine/IndexC.html**
- Family Village: **http://www.familyvillage.wisc.edu/med_altn.htm**
- Google: **http://directory.google.com/Top/Health/Alternative/**
- Healthnotes: **http://www.healthnotes.com/**

- MedWebPlus: **http://medwebplus.com/subject/Alternative_and_Complementary_Medicine**
- Open Directory Project: **http://dmoz.org/Health/Alternative/**
- HealthGate: **http://www.tnp.com/**
- WebMD®Health: **http://my.webmd.com/drugs_and_herbs**
- WholeHealthMD.com: **http://www.wholehealthmd.com/reflib/0,1529,00.html**
- Yahoo.com: **http://dir.yahoo.com/Health/Alternative_Medicine/**

The following is a specific Web list relating to hepatitis C virus; please note that any particular subject below may indicate either a therapeutic use, or a contraindication (potential danger), and does not reflect an official recommendation:

- **Herbs and Supplements**

  Interferon
  Source: Healthnotes, Inc.; www.healthnotes.com

General References

A good place to find general background information on CAM is the National Library of Medicine. It has prepared within the MEDLINEplus system an information topic page dedicated to complementary and alternative medicine. To access this page, go to the MEDLINEplus site at **http://www.nlm.nih.gov/medlineplus/alternativemedicine.html**. This Web site provides a general overview of various topics and can lead to a number of general sources.

CHAPTER 4. DISSERTATIONS ON HEPATITIS C VIRUS

Overview

In this chapter, we will give you a bibliography on recent dissertations relating to hepatitis C virus. We will also provide you with information on how to use the Internet to stay current on dissertations. **IMPORTANT NOTE:** When following the search strategy described below, you may discover non-medical dissertations that use the generic term "hepatitis C virus" (or a synonym) in their titles. To accurately reflect the results that you might find while conducting research on hepatitis C virus, we have not necessarily excluded non-medical dissertations in this bibliography.

Dissertations on Hepatitis C Virus

ProQuest Digital Dissertations, the largest archive of academic dissertations available, is located at the following Web address: **http://wwwlib.umi.com/dissertations**. From this archive, we have compiled the following list covering dissertations devoted to hepatitis C virus. You will see that the information provided includes the dissertation's title, its author, and the institution with which the author is associated. The following covers recent dissertations found when using this search procedure:

- **CD4+ T-helper cell responses in hepatitis C virus infection** by Day, Cheryl Liane, PhD from HARVARD UNIVERSITY, 2003, 219 pages
  http://wwwlib.umi.com/dissertations/fullcit/3091540
- **Design and synthesis of hepatitis C virus NS3 protease inhibitors** by Johansson, Anja, PhD from UPPSALA UNIVERSITET (SWEDEN), 2003, 79 pages
  http://wwwlib.umi.com/dissertations/fullcit/f286673
- **Development of peptide inhibitors of NS3a protease from hepatitis C virus (HCV)** by Portal Nunez, Sergio, Dr from UNIVERSIDAD DE NAVARRA (SPAIN), 2003, 166 pages
  http://wwwlib.umi.com/dissertations/fullcit/f204849
- **Epidemiology of hepatitis C virus infection among blood donors in northern Thailand** by Thaikruea, Lakkana, PhD from THE JOHNS HOPKINS UNIVERSITY, 2003, 152 pages
  http://wwwlib.umi.com/dissertations/fullcit/3080779

- **Modulation of antioxidant defenses and down regulation of heme oxygenase-1 by hepatitis C virus infection in vivo and hepatitis C protein expression in vitro** by Abdalla, Maher Yacoub, PhD from THE UNIVERSITY OF IOWA, 2003, 94 pages
  http://wwwlib.umi.com/dissertations/fullcit/3114332
- **Structural characterization of the hepatitis C virus core protein in its assembly pathway** by Kunkel, Meghan, PhD from THE UNIVERSITY OF TEXAS GRADUATE SCH. OF BIOMEDICAL SCI. AT GALVESTON, 2003, 127 pages
  http://wwwlib.umi.com/dissertations/fullcit/3113413
- **Tetraspanins, the hepatitis C virus and cell migration** by VanCompernolle, Scott Edward, PhD from KANSAS STATE UNIVERSITY, 2003, 100 pages
  http://wwwlib.umi.com/dissertations/fullcit/3100573
- **The cellular proteins that regulate hepatitis C virus RNA replication** by Gao, Lu, PhD from UNIVERSITY OF SOUTHERN CALIFORNIA, 2003, 167 pages
  http://wwwlib.umi.com/dissertations/fullcit/3103891

Keeping Current

Ask the medical librarian at your library if it has full and unlimited access to the *ProQuest Digital Dissertations* database. From the library, you should be able to do more complete searches via **http://wwwlib.umi.com/dissertations**.

CHAPTER 5. PATENTS ON HEPATITIS C VIRUS

Overview

Patents can be physical innovations (e.g. chemicals, pharmaceuticals, medical equipment) or processes (e.g. treatments or diagnostic procedures). The United States Patent and Trademark Office defines a patent as a grant of a property right to the inventor, issued by the Patent and Trademark Office.[8] Patents, therefore, are intellectual property. For the United States, the term of a new patent is 20 years from the date when the patent application was filed. If the inventor wishes to receive economic benefits, it is likely that the invention will become commercially available within 20 years of the initial filing. It is important to understand, therefore, that an inventor's patent does not indicate that a product or service is or will be commercially available. The patent implies only that the inventor has "the right to exclude others from making, using, offering for sale, or selling" the invention in the United States. While this relates to U.S. patents, similar rules govern foreign patents.

In this chapter, we show you how to locate information on patents and their inventors. If you find a patent that is particularly interesting to you, contact the inventor or the assignee for further information. **IMPORTANT NOTE:** When following the search strategy described below, you may discover non-medical patents that use the generic term "hepatitis C virus" (or a synonym) in their titles. To accurately reflect the results that you might find while conducting research on hepatitis C virus, we have not necessarily excluded non-medical patents in this bibliography.

Patents on Hepatitis C Virus

By performing a patent search focusing on hepatitis C virus, you can obtain information such as the title of the invention, the names of the inventor(s), the assignee(s) or the company that owns or controls the patent, a short abstract that summarizes the patent, and a few excerpts from the description of the patent. The abstract of a patent tends to be more technical in nature, while the description is often written for the public. Full patent descriptions contain much more information than is presented here (e.g. claims, references, figures, diagrams, etc.). We will tell you how to obtain this information later in the chapter.

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[8]Adapted from the United States Patent and Trademark Office:
http://www.uspto.gov/web/offices/pac/doc/general/whatis.htm.

The following is an example of the type of information that you can expect to obtain from a patent search on hepatitis C virus:

- **6-methylnicotinamide derivatives as antiviral agents**

  Inventor(s): Kim; Jong-Woo (Anyang-si, KR), Kim; Nam-Doo (Inchon-si, KR), Lee; Geun-Hyung (Anyang-si, KR), Lee; Hak-Dong (Anyang-si, KR), Lee; Jin-Soo (Anyang-si, KR), Lee; Sang-Wook (Anyang-si, KR), Park; Hee-Jeong (Anyang-si, KR), Park; Sang-Jin (Seoul, KR), Yoon; Sung-June (Seoul, KR)

  Assignee(s): Dong Wha Pharm. Ind. Co., Ltd. (Seoul, KR)

  Patent Number: 6,608,058

  Date filed: October 10, 2002

  Abstract: The present invention relates to novel 6-methylnicotinamide derivatives and their pharmaceutically acceptable salts, the process for preparing them, and the pharmaceutical compositions containing said compounds as active ingredients. The 6-methylnicotinamide derivatives of the present invention exhibit their inhibitory activity against the proliferation of human immunodeficiency virus (HIV) as well as hepatitis B virus (HBV) and **hepatitis C virus** (HCV), such that they can be used for hepatitis B, hepatitis C and acquired immune deficiency syndrome (AIDS).

  Excerpt(s): This patent application claims a benefit of priority from Korean Patent Application No. 2000/20137 filed Apr. 17, 2000 and Korean Patent Application No. 2000/31926 filed Jun. 10, 2000 through PCT Application Serial No. PCT/KRO1/00613 filed Apr. 13, 2001, the contents of each of which are incorporated herein by reference. Hepatitis B virus (HBV; referred as "HBV" hereinafter) causes acute or chronic hepatitis, which may progress to liver cirrhosis and liver cancer. It is estimated that three hundred million people are infected with HBV in the world (Tiollais & Buendia, Sci. Am., 264, 48, 1991). There has been much research about the molecular biological characteristics of HBV and their relationship to liver diseases in order to find ways to prevent and treat hepatitis B. Various vaccines and diagnostic drugs have been developed and much effort is being channeled into research to find treatment for hepatitis B. The gene for HBV polymerase comprises 80% of the whole virus genome and produces a protein of 94 kD size with 845 amino acids, which has several functions in the replication of virus genome. This polypeptide includes sequences responsible for activities of protein primer, RNA dependent DNA polymerase, DNA dependent DNA polymerase, and RNase H. Kaplan and his coworkers first discovered reverse transcriptase activities of polymerase, which led to much research in replicating mechanism of HBV.

  Web site: http://www.delphion.com/details?pn=US06608058__

- **Activation of HCV-specific T cells**

  Inventor(s): Houghton; Michael (Danville, CA), Paliard; Xavier (San Francisco, CA), Selby; Mark (San Francisco, CA)

  Assignee(s): Chiron Corporation (Emeryville, CA)

  Patent Number: 6,562,346

  Date filed: October 27, 2000

  Abstract: The invention provides a method of activating **hepatitis C virus** (HCV)-specific T cells, including CD4.sup.+ and CD8.sup.+ T cells. HCV-specific T cells are

activated using fusion proteins comprising HCV NS3, NS4, NS5a, and NS5b polypeptides, polynucleotides encoding such fusion proteins, or polypeptide or polynucleotide compositions containing the individual components of these fusions. The method can be used in model systems to develop HCV-specific immunogenic compositions, as well as to immunize a mammal against HCV.

Excerpt(s): The invention relates to the activation of hepatitis C virus(HCV)-specific T cells. More particularly, the invention relates to the use of multiple HCV polypeptides, either alone or as fusions, to stimulate cell-mediated immune responses, such as to activate HCV-specific T cells. Hepatitis C virus (HCV) infection is an important health problem with approximately 1% of the world's population infected with the virus. Over 75% of acutely infected individuals eventually progress to a chronic carrier state that can result in cirrhosis, liver failure, and hepatocellular carcinoma. See Alter et al. (1992) N. Engl. J. Med. 327:1899-1905; Resnick and Koff. (1993) Arch. Intem. Med. 153:1672-1677; Seeff (1995) Gastrointest. Dis. 6:20-27; Tong et al. (1995) N. Engl. J. Med. 332:1463-1466. Despite extensive advances in the development of pharmaceuticals against certain viruses like HIV, control of acute and chronic HCV infection has had limited success (Hooffiagle and di Bisceglie (1997) N. Engl. J. Med. 336:347-356). In particular, generation of a strong cytotoxic T lymphocyte (CTL) response is thought to be important for the control and eradication of HCV infections. Thus, there is a need in the art for effective methods of inducing strong CTL responses against HCV.

Web site: http://www.delphion.com/details?pn=US06562346__

- **Adsorbent for eliminating hepatitis C virus, adsorber, and adsorption method**

  Inventor(s): Asahi; Takashi (Kobe, JP), Kaneko; Shuichi (Kanazawa, JP), Nomura; Michio (Kakogawa, JP), Ogino; Eiji (Kobe, JP), Sakai; Akito (Kanazawa, JP)

  Assignee(s): Kaneka Corporation (Osaka, JP)

  Patent Number: 6,600,014

  Date filed: November 9, 1999

  Abstract: An adsorbent for removing **hepatitis C virus** which has the ability to adsorb HCV particles, particularly immune-complex HCV particles, from a patient's body blood safely and with high efficiency and high selectivity for enhancing the efficacy of interferon therapy, an HCV adsorption apparatus including said adsorbent, and a adsorbing method for removing HCV are provided.An adsorbent for removing **hepatitis C virus** which comprises a compound capable of adsorbing **hepatitis C virus** as immobilized on a water-insoluble carrier, an adsorption apparatus including said adsorbent, and an adsorbing method for removing HCV.

  Excerpt(s): The present invention relates to an adsorbent for removing **hepatitis C virus** which is capable of selectively adsorbing **hepatitis C virus** from body fluids such as blood, plasma, etc. to thereby expedite the cure for hepatitis C, an adsorption apparatus including said adsorbent, and an adsorbing method for removing **hepatitis C virus.** With the successful cloning of the RNA virus genome of **hepatitis C virus** in 1989 (Q. L. Choo et al.: Science, 244, 359, 1989), it became possible to assay anti-hepatitis C virus antibody using a recombinant protein. As a result, most of the hepatitis termed non-A, non-B hepatitis in the past were found to be hepatitis C. Thus, it is estimated that in Japan today there are about 2,000,000 HCV carriers and, of them, 1,400,000 have chronic hepatitis and 300,000 have cirrhosis (Shiro Iino: Medical Practice in Gastroenterology-2, Hepatitis C, 11-17, 1993). According to the Ministry of Health and welfare demographic

statistics, the number of deaths due to primary liver cancer in 1992 was 27 thousand (1992 Demographic Statistics, Minister of Health and Welfare Statistical Information Bureau, Vol. 1, 1993) and approximately 70% of the casualties were due to hepatocellular carcinoma associated with **hepatitis C virus** infection and it is by now considered that this cancer ensues following the progression of chronic hepatitis to cirrhosis (S. Kaneko et al.: Intervirology, 37, 108, 1994; Eiki Matsushita et al.: Japanese Journal of Clinics, 53, 727, 1995 Special Issue). Therefore, hepatitis C can be said to be a refractory disease which progresses to cirrhosis to hepatocellular carcinoma.

Web site: http://www.delphion.com/details?pn=US06600014__

- **Antigenic structural peptide, antigenic and immunogenic compounds, and uses for detecting, preventing and treating an HCV infection**

  Inventor(s): Dalbon; Pascal (Lyons, FR), Jolivet; Michel (Bron, FR), Lacoux; Xavier (Lyons, FR), Ladaviere; Laurent (Villeurbanne, FR), Penin; Fran.cedilla.ois (Decines, FR)

  Assignee(s): Bio Merieux (Marcy l'Etoile, FR)

  Patent Number: 6,576,240

  Date filed: September 7, 1999

  Abstract: The invention concerns a structural peptide, identified by antibodies directed against a polypeptide, comprising the 2-45 amino acid sequence of the N-terminal end of the Core or nucleocapsid (p21) protein of the **hepatitis C virus** (HCV), excluding any protein or peptide compound comprising or consisting of the N-terminal end. The invention is characterized in that it comprises a tertiary structure consisting of at least a first peptide fragment having a secondary structure in.alpha. helix, a second peptide fragment having secondary structure in.alpha. helix and a third peptide bond fragment linking the two.alpha. helices, these two.alpha. helices being substantially perpendicular to each other in space. This peptide can be used for detecting antibodies directed against the p21 protein of HCV, for detecting all of part of the RNA of HCV and for preparing a diagnostic, prophylactic or therapeutic composition for detecting, preventing or treating an HCV infection.

  Excerpt(s): The present invention relates to the characterization of an antigenic site belonging to an immuno-dominant multiepitope region located in the N-terminal end of the Core or nucleocapsid protein (or p21 protein) of the **hepatitis C virus** (HCV), [B. Hosein et al., Proc. Natl. Acad. Sci. USA, 88, 3647-51 (1991)] as well as to the applications resulting therefrom, in particular in the diagnosis, treatment or prevention of an HCV infection. In accordance with the document EP-A-0 569 309, in the name of the Applicant, a peptide is known which extends from the amino acid at position 2 to the amino acid at position 45 of the N-terminal end of the HCV nucleocapsid protein, and whose sequence is identified by SEQ ID NO: 1. This peptide determines an immunodominant region which is sufficient, on its own, for obtaining the same sensitivity and specificity, in terms of detection of antibodies directed against HCV, as with the nucleocapsid protein in its entirety. this immunodominant epitope is of conformational type, and corresponds to a three-dimensional unit of helix-loop or elbow-helix type, in which the two helices are arranged substantially perpendicularly to each other.

  Web site: http://www.delphion.com/details?pn=US06576240__

- **Compositions and methods for treatment of hepatitis C virus-associated diseases**

  Inventor(s): Anderson; Kevin P. (Carlsbad, CA), Hanecak; Ronnie C. (San Clemente, CA), Nozaki; Chikateru (Kumamoto, JP)

  Assignee(s): ISIS Pharmaceuticals, Inc. (Carlsbad, CA)

  Patent Number: 6,608,191

  Date filed: October 18, 2000

  Abstract: Antisense oligonucleotides are provided which are complementary to and hybridizable with at least a portion of HCV RNA and which are capable of inhibiting the function of the HCV RNA. These oligonucleotides can be administered to inhibit the activity of **Hepatitis C virus** in vivo or in vitro. These compounds can be used either prophylactically or therapeutically to reduce the severity of diseases associated with **Hepatitis C virus,** and for diagnosis and detection of HCV and HCV-associated diseases. Methods of using these compounds are also disclosed.

  Excerpt(s): This invention relates to the design and synthesis of antisense oligonucleotides which can be administered to inhibit the activity of **Hepatitis C virus** in vivo or in vitro and to prevent or treat Hepatitis C virus-associated disease. These compounds can be used either prophylactically or therapeutically to reduce the severity of diseases associated with **Hepatitis C virus.** These compounds can also be used for detection of **Hepatitis C virus** and diagnosis of Hepatitis C virus-associated diseases. Oligonucleotides which are specifically hybridizable with **Hepatitis C virus** RNA targets and are capable of inhibiting the function of these RNA targets are disclosed. Methods of using these compounds are also disclosed. The predominant form of hepatitis currently resulting from transfusions is not related to the previously characterized Hepatitis A virus or Hepatitis B virus and has, consequently, been referred to as Non-A, Non-B Hepatitis (NANBH). NANBH currently accounts for over 90% of cases of post-transfusion hepatitis. Estimates of the frequency of NANBH in transfusion recipients range from 5%-13% for those receiving volunteer blood, or 25-54% for those receiving blood from commercial sources. Acute NANBH, while often less severe than acute disease caused by Hepatitis A or Hepatitis B viruses, can lead to severe or fulminant hepatitis. Of greater concern, progression to chronic hepatitis is much more common after NANBH than after either Hepatitis A or Hepatitis B infection. Chronic NANBH has been reported in 10%-70% of infected individuals. This form of hepatitis can be transmitted even by asymptomatic patients, and frequently progresses to malignant disease such as cirrhosis and hepatocellular carcinoma. Chronic active hepatitis, with or without cirrhosis, is seen in 44%-90% of posttransfusion hepatitis cases. Of those patients who developed cirrhosis, approximately one-fourth died of liver failure.

  Web site: http://www.delphion.com/details?pn=US06608191__

- **Compositions of hepatitis C virus NS3/NS4A complex and methods for crystallizing same**

  Inventor(s): Prosise; Winifred W. (Ramsey, NJ), Reichert; Paul (Montville, NJ), Taremi; Shahriar Shane (Upper Montclair, NJ), Weber; Patricia C. (Yardley, PA), Yao; Nanhua (Edison, NJ)

  Assignee(s): Schering Corporation (Kenilworth, NJ)

  Patent Number: 6,524,589

  Date filed: April 5, 2000

  Abstract: The invention relates to the purification and crystallization of **hepatitis C virus** (HCV) NS3/NS4A polypeptide complex. Also, crystallization conditions for NS3/NS4A are provided. Further, the atomic coordinates for the NS3/NS4A protein are disclosed. Examples of its use for the determination of the three-dimensional atomic structures of HCV NS3/NS4A with substrate(s) or substrate analog(s) or inhibitor complexes are also provided.

  Excerpt(s): The present invention relates to crystalline HCV NS3/NS4A complex, the structure of HCV NS3/NS4A complex as determined by X-ray crystallography, the use of that structure to solve the structure of HCV NS3, NS3/NS4A complex homologues and other crystal forms of the HCV NS3/NS4A complex, mutants and co-complexes thereof and the use of HCV NS3/NS4A complex, mutants and co-complexes thereof to design inhibitors of HCV NS3/NS4A complex. The **hepatitis C virus** causes one of the world's most pandemic and insidious diseases. According to the World Health Organization, there are approximately 170 million HCV carriers worldwide with prevalence up to 0.5-10% (Release:, 1998), and in the United States, four million individuals are **hepatitis C virus** carriers (Alter and Mast, 1994). The **hepatitis C virus** (HCV) was identified in 1989 and accounted for 50-60% of the non-A, non-B transfusion associated hepatitis (Alter et al N Engl J Med 321:1494-1500 (1989); Choo, et al., Science 244:359-362 (1989); Kuo, et al., Science 244:362-364 (1989)). To date, interferon-alpha monotherapy and interferon-alpha-2b and ribavirin combination therapy (Rebetron, Schering-Plough, Kenilworth, N.J.) are the only approved treatments. Twenty percent of the patients responded to interferon-.alpha. monotherapy and 42% of the patients responded to Rebetron combination therapy (Reichard, et al., Lancet 351:83-87 (1998)). It is important to develop more effective antiviral agents against the various viral targets in order to effectively combat the disease. In spite of these different functions during the HCV life cycle, there is no evidence that the NS3 protease and helicase are ever separated from one another in HCV infected cells. Likewise, only the 70 kDa NS3 protein containing both the protease and helicase domains has ever been detected in cells transfected with recombinant vaccinia expressing HCV nonstructural proteins (Grakoui, et al., J Virol 67:1385-1395 (1993)). In addition, NS3 has been found to spontaneously associate with NS4A to form a stable noncovalent NS3/NS4A complex in vivo (Failla, et al., J Virol 69:1769-1777 (1995); Grakoui, et al., J Virol 67:1385-1395 (1993)). The covalent fusion of the protease and helicase domains in NS3 as well as the spontaneous formation of a complex with NS4A suggests that there may be functional dependence between these polypeptides to achieve additional activities other than the fundamental enzymatic properties.

  Web site: http://www.delphion.com/details?pn=US06524589__

- **Conserved motif of hepatitis C virus E2/NS1 region**

  Inventor(s): Houghton; Michael (Danville, CA), Weiner; Amy J. (Benicia, CA)

  Assignee(s): Chiron Corporation (Emeryville, CA)

  Patent Number: 6,692,907

  Date filed: May 9, 1995

  Abstract: The hypervariable region (E2HV) of the putative **hepatitis C virus** (HCV) glycoprotein E2/NS1, between about amino acid 384 to about amino acid 414, is a rapidly evolving region of HCV, and is likely to be under positive immune selection. A newly discovered motif within this hypervariable region is immunogenic and conserved with respect to the character of the amino acids. In many isolates, this motif falls between amino acids 401 to 406 or 407. The discovery of this motif allows for additional materials and methods to treat and diagnose HCV.

  Excerpt(s): This invention relates generally to the field of **hepatitis C virus** (HCV) and, more specifically, to the discovery of an immunologically important motif in the E2/NS1 region. Hepatitis C virus (HCV) has been identified as the major causative agent of post-transfusion non-A, non-B hepatitis (NANBH). Materials and methods for obtaining the viral genomic sequences are known. See, e.g., PCT Publ. Nos. WO89/04669, WO90/11089, and WO90/14436. For general information about HCV, see Houghton et al. (1991), Hepatology 14:381-388. Molecular characterization of the HCV genome indicates that it is a RNA molecule of positive polarity containing approximately 9,500 nucleotices comprising a long translational open-reading frame (ORF) that could encode a large polypeptide of approximately 3000 amino acids (aa) beginning with the first in-frame methionine codon. A hypervariable domain located at the amino terminus of the putative envelope glycoprotein E2/NS1 (also called E2) has been located, see PCT Publ. No. WO93/016126; Weiner et al. (1991), Virology 180:842-48; Weiner et al (1992), Proc. Natl. Acad. Sci. USA 89:3468-72; Weiner et al. (1992), Vaccines 92:303-08, Cold Spring Harbor Laboratory.

  Web site: http://www.delphion.com/details?pn=US06692907__

- **Diagnosis method of inflammatory, fibrotic or cancerous disease using biochemical markers**

  Inventor(s): Poynard; Thierry (Paris, FR)

  Assignee(s): Assistance Publique-Hopitaux de Paris (AP-HP) (Paris, FR)

  Patent Number: 6,631,330

  Date filed: October 13, 2000

  Abstract: The present invention is drawn to a new diagnosis method for detecting the extend of a inflammatory, fibrotic or cancerous disease in a patient, in particular liver fibrosis, in particular in a patient infected with **hepatitis C virus,** by using the serum concentration of easily detectable biological markers. The invention is also drawn to diagnosis kits for the implementation of the method.

  Excerpt(s): The present invention is drawn to a new diagnosis method for detecting the extend of a inflammatory, fibrotic or cancerous disease in a patient, in particular liver fibrosis, in particular in a patient-infected with **hepatitis C virus,** by using the serum concentration of easily detectable biological markers. The invention is also drawn to diagnosis kits for the implementation of the method. Liver biopsy is considered as

mandatory for the management of patients infected by the **hepatitis C virus** (HCV), particularly for the staging of fibrosis (1-4). For patients and general practitioner it can be considered as an aggressive procedure (5-6). Numerous studies have shown significant predictive values of several markers for the diagnosis of cirrhosis (6-15) but none for the diagnosis of earlier stage as few septa (beginning of bridging fibrosis), prospectively in a large population infected only by HCV virus. It is nevertheless important to be able to detect these early stages in the development of liver pathology, in order to improve the patient treatment, and the follow-up of the disease. As liver biopsy is still an invasive procedure, it could be advantageous to have a fast and easy to perform test that would give a good predictive value of the level of fibrosis in the patient.

Web site: http://www.delphion.com/details?pn=US06631330__

- **Efficient hepatitis C virus replicon and its use in identifying antiviral compounds**

  Inventor(s): Hahm; Bumsuk (San Diego, CA), Jang; Sung Key (Kyungbuk, KR), Liang; Chengyu (Stony Brook, NY), Wimmer; Eckard (East Setauket, NY)

  Assignee(s): The Research Foundation of the State University of New York (Albany, NY)

  Patent Number: 6,689,559

  Date filed: November 29, 2001

  Abstract: The present invention provides a **Hepatitis C Virus** (HCV) replicon that efficiently replicates in an eukaryotic cell. The HCV replicon includes a nucleic acid sequence encoding a subgenomic fragments of HCV of any genotype that confer on the RNA the ability to replicate, and a nucleic acid sequence encoding an acetyl transferase selectable marker, such as puromycin. Also provided is an HCV type 1a replicon that efficiently replicates in an eukaryotic cell and includes a nucleic acid sequence encoding subgenomic fragments of type 1a HCV that confer on the RNA the ability to replicate, and a nucleic acid sequence encoding a acetyl transferase selectable marker. Further provided are eukaryotic cell lines that include an HCV replicon or an HCV type 1a replicon which efficiently replicate in the eukaryotic cell. The present invention also provides screening methods for identifying candidate compounds that inhibit the propagation of HCV.

  Excerpt(s): The **hepatitis C virus** (HCV) is the sole member of the genus Hepacivirus of the family Flaviviridae, which also includes the Flavivirus, yellow fever virus and the Pestivirus, bovine viral diarrhea virus. Since the discovery of HCV in 1989, the viral genome has been well characterized. The genome is a positive-sense single-stranded RNA of about 9.3 kb, that consists of a single open reading frame (ORF) and nontranslated regions (NTRs) at the 5' and 3' ends (Bartenschlager and Lohmann, 2000). The 5'NTR is highly structured and contains an internal ribosomal entry site (IRES) that mediates cap-independent translation of the viral polyprotein. The 3'NTR is tripartite and is composed of a short variable region (.about.21-39 nucleotides), a poly (U) tract of variable length, and a highly conserved terminal sequence of 98 nucleotides. The ORF of HCV is translated into a polyprotein (i.e., NH.sub.2 -core-E1-E2-p7-NS2-NS3-NS4A-NS4B-NS5A-NS5B-COOH) that is co-translationally and posttranslationally processed by host cell and viral proteases into at least 10 distinct products. The core and envelope (E1 and E2) proteins are the major viral constituents of the virus particle while the remainder, the non-structural (NS) proteins, are required for virus replication.

  Web site: http://www.delphion.com/details?pn=US06689559__

- **HCV-derived RNA polymerase gene**

  Inventor(s): Higashi; Kazuhiro (Hyogo, JP), Kohara; Kyoko (Chiba, JP), Kohara; Michinori (Chiba, JP), Toyoda; Tetsuya (1339-4, Tsubukuhonmachi, Kurume-shi, Fukuoka 830-0047, JP), Tsuchiya; Masayuki (Shizuoka, JP)

  Assignee(s): Chugai Seiyaku Kabushiki Kaisha (Tokyo, JP), International Reagents Corporation (Hyogo, JP), Toyoda; Tetsuya (Fukuoka, JP)

  Patent Number: 6,639,053

  Date filed: December 21, 2001

  Abstract: The present invention provides a gene encoding an RNA polymerase which plays an important role in the reproduction of **hepatitis C virus,** and a method of screening using this gene or this RNA polymerase protein, thereby allowing easy performance of screening for substances which inhibit the RNA polymerase playing an important role in HCV reproduction.

  Excerpt(s): This application is a 371 of PCT/JP99/03381, filed Jun. 24, 1999. The present invention relates to an RNA polymerase gene derived from **hepatitis C virus** (referred to as "HCV" herein), a method of screening using this gene or this RNA polymerase protein, and a substance able to be isolated by this screening method. Generally known viral hepatitis includes hepatitis A which is mainly orally transmitted, and hepatitis B transmitted by means of the blood. Moreover, apart from these hepatitis, there is hepatitis called non-A, non-B hepatitis which is transmitted by means of blood transfusion. Since most of these infected with non-A, non-B hepatitis become chronic, and the incidence of development into cirrhosis and hepatoma is high, this is one disease for which the establishment of a certain means of treatment is urgently sought.

  Web site: http://www.delphion.com/details?pn=US06639053__

- **Hepatitis C assay utilizing recombinant antigens**

  Inventor(s): Casey; James M. (4110 Bayside Ct., #2C, Zion, IL 60099), Dailey; Stephen H. (472 Tyler Ct., Vernon Hills, IL 60061), Dawson; George J. (914 S. Dymond Rd., Libertyville, IL 60048), Desai; Suresh M. (1408 Amy La., Libertyville, IL 60048), Devare; Sushil G. (2492 Farnsworth La., Northbrook, IL 60062), Gutierrez; Robin A. (34859 N. Hunt Club Rd., Gumee, IL 60031), Lesniewski; Richard R. (8706 110th Ave., Kenosha, WI 53142), Rupprecht; Kevin R. (720 Durham La., Grayslake, IL 60030), Stewart; James L. (4422 Sheffield Ct., Gumee, IL 60031)

  Assignee(s): none reported

  Patent Number: 6,593,083

  Date filed: October 17, 2000

  Abstract: Unique recombinant antigens representing distinct antigenic regions of the **Hepatitis C Virus** (HCV) genome which can be used as reagents for the detection of antibodies and antigen in body fluids from individuals exposed to HCV. The present invention also provides an assay for detecting the presence of an antibody to an HCV antigen in a sample by contacting the sample with the recombinant antigens. Preferred assay formats include a screening assay, a confirmatory assay, a competition or neutralization assay and an immunodot assay.

Excerpt(s): This invention relates generally to an assay for identifying the presence in a sample of an antibody which is immunologically reactive with a **hepatitis C virus** antigen and specifically to an assay for detecting a complex of an antibody and recombinant antigens representing distinct regions of the HCV genome. Recombinant antigens derived from the molecular cloning and expression in a heterologous expression system of the synthetic DNA sequences representing distinct antigenic regions of the HCV genome can be used as reagents for the detection of antibodies and antigen in body fluids from individuals exposed to **hepatitis C virus** (HCV). Acute viral hepatitis is clinically diagnosed by a well-defined set of patient symptoms, including jaundice, hepatic tenderness, and an increase in the serum levels of alanine aminotransferase (ALT) and aspartate aminotransferase. Additional serologic immunoassays are generally performed to diagnose the specific type of viral causative agent Historically, patients presenting clinical hepatitis symptoms and not otherwise infected by hepatitis A, hepatitis B, Epstein-Barr or cytomegalovirus were clinically diagnosed as having non-A non-B hepatitis (NANBH) by default. The disease may result in chronic liver damage. Each of the well-known, immunologically characterized hepatitis-inducing viruses, hepatitis A virus (HAV), hepatitis B virus (HBV), and hepatitis D virus (HDV) belongs to a separate family of viruses and has a distinctive viral organization, protein structure, and mode of replication.

Web site: http://www.delphion.com/details?pn=US06593083__

- **Hepatitis C diagnostics and vaccines**

  Inventor(s): Cho; Joong Myung (Seoul, KR), Choi; Deog Young (Daejeon, KR), Kim; Chun Hyung (Daejeon, KR), Kim; Sung Taek (Daejeon, KR), Lee; Yong Beom (Daejeon, KR), Lim; Kook Jin (Seoul, KR), Park; Young Woo (Deajeon, KR), So; Hong Seob (Daejeon, KR), Yang; Jae Young (Daejeon, KR)

  Assignee(s): Lucky Limited (KR)

  Patent Number: 6,538,126

  Date filed: April 20, 1994

  Abstract: The present invention provides polynucleotides derived from cDNA of novel type of **hepatitis C virus** named Korean type **hepatitis C virus** (KHCV), polypeptides encoded therein, and antibodies directed against the polypeptides; and also provide diagnostics and vaccines employing any of the above materials as active ingredient(s).

  Excerpt(s): The present invention relates to polynucleotides derived from cDNA of a novel type of **hepatitis C virus** Korean type **hepatitis C virus** (KHCV), polypeptides encoded therein and antibodies directed against the polypeptides; and to diagnostics and vaccines employing any of these reagents, i.e., said polynucleotides, polypeptides and antibodies, as an active ingredient. In general, virus-induced hepatitis has been known to be caused by various hepatitis viruses including hepatitis A virus, hepatitis B virus, hepatitis delta virus, hepatitis E virus, Cytomegalo virus and Esptein-Barr virus; and the genotypes of the viruses have been discovered since 1980, facilitating the development of diagnostics, vaccines and therapeutic agents. Further, it has been discovered that a new type of hepatitis nicknamed as non-A non-B or C hepatitis, accounts for 80 to 90% of hepatitis caused by blood transfusion (Lancet, 2, 838-841 (1975)); and such post-transfusion hepatitis frequently progresses to cirrhosis or hepatocellular carcinoma up to about 50%.

  Web site: http://www.delphion.com/details?pn=US06538126__

- **Hepatitis C virus culture system**

  Inventor(s): Bartenschlager; Ralf (Nachdem Alten Schloss 22, D-55239 Gau-Odernheim, DE)

  Assignee(s): none reported

  Patent Number: 6,630,343

  Date filed: March 31, 2000

  Abstract: The **hepatitis C virus** (HCV) cell culture system according to the invention consists of human hepatoma cells, which are transfected with a HCV-RNA construct, that comprises the HCV specific RNA segments 5'to NTR, NS3, NS4A, NS4B, NS5A, NS5B, and 3'to NTR as well as a minimum of one marker gene for selection (selection gene).

  Excerpt(s): The invention relates to a **hepatitis C virus** (HCV) cell culture system, which comprises mainly eukaryotic cells containing transfected HCV specific genetic material, which means they are transfected with HCV specific genetic material. The **hepatitis C virus** (HCV) is one of the main causes worldwide of chronic and sporadic liver diseases. The history of most HCV infections does not involve any obvious clinical signs, but 80-90% of the infected people become chronic carriers of the virus and 50% of these chronic carriers of the virus develop chronic hepatitis with different degrees of severity. Approx. 20% of the chronically infected develop a cirrhosis of the liver over 10 to 20 years, based on what a primary hepatocellular carcinoma can develop. Nowadays chronic hepatitis C is the main indication for liver transplantation. One currently available therapy involves high-dose administration of Interferon alpha or a combination of Interferon alpha and the purine nucleoside analogue Ribavirin. However, only approx. 60% of all treated persons respond to this therapy and with these, a new viraemia occurs in more than half of all cases after the discontinuation of the treatment. Due to the high prevalence, especially in industrialized countries, the serious effects of chronic infections and the lack of effective therapy, the development of a HCV specific chemotherapy is an important goal of pharmaceutical research and development. Such a goal, however, has been hampered by the lack of a suitable cell culture system, which enables the study of virus replication and pathogenesis in eukaryotic cells.

  Web site: http://www.delphion.com/details?pn=US06630343__

- **Host derived proteins binding HCV: medical, diagnostic and purification use**

  Inventor(s): Depla; Erik (Destelbergen, BE), Maertens; Geert (Bruges, BE)

  Assignee(s): N.V. Innogenetics (Ghent, BE)

  Patent Number: 6,670,114

  Date filed: May 5, 2000

  Abstract: The finding that the human proteins annexin V, tubulin and apolipoprotein B bind to the **hepatitis C virus** envelope proteins E1 and/or E2 and the usage of these human proteins to diagnose and treat an infection with **hepatitis C virus** are described. The usage of the latter proteins to enrich HCV envelope proteins and molecules which inhibit binding of HCV to these human proteins, as well as vaccines employing the E1 and/or E2 binding domains are also disclosed.

Excerpt(s): The present invention is based on the development of an efficient infection system for HCV, and on the finding that the human proteins annexin V, tubulin and apolipoprotein B bind to the **hepatitis C virus** envelope proteins E1 and/or E2 and concerns the usage of these human proteins to diagnose and treat an infection with **hepatitis C virus.** The present invention also relates to the usage of the latter proteins to enrich HCV envelope proteins and to molecules which inhibit binding of HCV to these human proteins, as well as vaccines employing the E1 and/or E2 binding domains. Hepatitis C virus (HCV) infection is a major health problem in both developed and developing countries. It is estimated that about 1 to 5% of the world population is affected by the virus, amounting up to 175 million chronic infections worldwide. HCV infection appears to be the most important cause of transfusion-associated hepatitis and frequently progresses to chronic liver damage. Moreover, there is evidence implicating HCV in induction of hepatocellular carcinoma. Consequently, the demand for reliable diagnostic methods and effective therapeutic measures is high. Also sensitive and specific screening methods for HCV-contaminated blood-products and improved methods to culture HCV are needed. Standardized infections of live viruses are a prerequisite for studying the binding parameters of HCV to eukaryotic cells. Controllable infection of eukaryotic cells by HCV, however, poses a problem. As a partial solution to this problem, a Daudi cell line was selected, which was supporting productive infection for HCV (Shimizu et al., 1996). However, the inocula for infection gave variable results in Molt-4 cells and even in Daudi cells. Consequently, comparative studies, e.g. on the development of drugs interfering with the interaction of HCV with its target eukaryotic cell are troublesome. Therefore, there is an urgent need for a protocol, which guarantees efficient and reliable infections of eukaryotic cells by HCV.

Web site: http://www.delphion.com/details?pn=US06670114__

- **Human monoclonal antibodies specific for hepatitis C virus (HCV) E2 antigen**

  Inventor(s): Allander; Tobias Erik (Stockholm, SE), Persson; Mats Axel Atterdag (Stockholm, SE)

  Assignee(s): Karolina Innovations AB (Stockholm, SE)

  Patent Number: 6,538,114

  Date filed: April 19, 1996

  Abstract: The present invention relates to compositions derived from immunoglobulin molecules specific for the **hepatitis C virus** (HCV). More particularly, the invention is related to molecules which are capable of specifically binding with HCV E2 antigen. The molecules are useful in specific binding assays, affinity purification schemes and pharmaceutical compositions for the prevention and treatment of HCV infection in mammalian subjects. The invention thus relates to novel human monoclonal antibodies specific for HCV E2 antigen, fragments of such monoclonal antibodies, polypeptides having structure and function substantially homologous to antigen-binding sites obtained from such monoclonal antibodies, nucleic acid molecules encoding those polypeptides, and expression vectors comprising the nucleic acid molecules.

  Excerpt(s): The present invention relates to compositions derived from immunoglobulin molecules specific for the **hepatitis C virus** (HCV). More particularly, the invention is related to recombinant human monoclonal antibodies which are capable of specifically binding with HCV E2 antigen. Hepatitis C virus (HCV) infection occurs throughout the world and is the major cause of transfusion-associated hepatitis. There are an estimated 150,000 new cases of HCV infection each year in the United States. The seroprevalence

of anti-HCV antibodies in blood donors from around the world has been shown to vary between 0.02 and 1.23%, with rates in some countries as high as about 19%. In addition to being the predominate cause of transfusion-induced hepatitis, HCV is also a common cause of hepatitis in individuals exposed to blood or blood products. Thus, recipients of blood or blood products, intravenous drug users, renal dialysis patients and needle-stick victims represent high-risk groups for HCV infection. Alter et al. (1993) Infect Agents Dis 2:155-166. Further, heterosexual transmission of HCV across the urogenital tract, and mother-to-baby transmission, has been well documented. Ohto et al. (1994) N Engl J Med 330:744-750. Other risk factors associated with HCV infection include familial or household contact with an HCV-infected individual and health-care employment with occupational exposure to blood and hemodialysis. Alter et al. (1990) JAMA 264:2231-2235. Chronic hepatitis develops in approximately 62% of infections. Alter et al. (1992) N Engl J Med 327:1899-1905. Most of the serious liver disease associated with HCV results from the high propensity of the agent to cause chronic, persistent infection. Cirrhosis occurs in approximately 20% of chronic cases, of which 20 to 25% will result in liver failure. Another serious sequela associated with HCV infection is primary hepatocellular carcinoma.

Web site: http://www.delphion.com/details?pn=US06538114__

- **Method for measurement of hepatitis C virus**

  Inventor(s): Aoyagi; Katsumi (Wako, JP), Iida; Kumiko (Wako, JP), Ohue; Chiharu (Wako, JP), Yagi; Shintaro (Wako, JP)

  Assignee(s): Advanced Life Science Institute, Inc. (Saitama, JP)

  Patent Number: 6,623,921

  Date filed: April 26, 2002

  Abstract: A method for measurement of the **hepatitis C virus** (HCV) characterized by measuring HCV core antigen and HCV core antibody by their binding with probes in the presence of an anionic surfactant or a non-ionic surfactant, or both.

  Excerpt(s): The present invention relates to a method for detection of the **hepatitis C virus** (HCV), and more specifically it relates to a method for measurement of HCV core antigen or for simultaneous measurement of HCV core antigen and HCV core antibodies. The method is particularly effective for screening of multiple blood samples and the like. Hepatitis caused by infection with HCV (**hepatitis C virus**) becomes chronic with high incidence, and as the infection period is prolonged it often progresses to liver cirrhosis and hepatocellular carcinoma. However, since infection with HCV occurs mainly through blood and blood-derived components, it is possible to identify and eliminate the source of infection to block the infection route. Current methods of identifying infection sources are primarily methods of detecting antibodies against HCV polypeptides, but methods are being sought that can identify infection sources with greater accuracy. Such methods are being sought because of the existence of a period of time known as the "window period" after HCV infection during which the antigen is present but antibodies are not yet produced. Antibody testing cannot determined whether serum taken during this period is infected or not. Therefore, there is a risk of secondary infection by the blood derived components, such as blood donation, blood components, factors from blood, contaminated specimens in the window period, because blood donor is screened by the antibody test that can not exclude such specimens. For this reason it has been necessary to detect HCV itself, that is, HCV particles, instead of antibodies against HCV polypeptides to reduce the risk.

Web site: http://www.delphion.com/details?pn=US06623921__

- **Method for removing and reducing hepatitis C virus**

  Inventor(s): Sawada; Kouji (Kashiba, JP), Shimoyama; Takashi (Kobe, JP)

  Assignee(s): Japan Immunoresearch Laboratories Co., Ltd. (Gunma, JP)

  Patent Number: 6,713,252

  Date filed: June 27, 2002

  Abstract: Described is a method of removing and reducing HCV from the blood of an HCV-infected patient, which comprises carrying out, once a day for at least 5 straight days, a treatment of bringing the blood into contact with an adsorptive carrier having a higher affinity for infected, activated and/or defective leukocytes than for uninfected leukocytes. The treatment according to the present invention makes it possible to markedly reduce the blood HCV level of a patient suffering from Hepatitis C, thereby enabling antiviral therapy, for example, treatment with interferon. This brings a drastic improvement in the cure rate for Hepatitis C.

  Excerpt(s): The present invention relates to a method for removing and reducing **Hepatitis C virus** (HCV) in the blood of patients infected with HCV; and a method for treating HCV infectious diseases. Hepatitis C is a viral infection of the liver having a high risk of progressing to cirrhosis or liver cancer. After HCV, which is causative of Hepatitis C, infects cells, for example liver cells, it harbors in these cells and leukocytes during the incubation period. Apheresis has recently been employed for the purpose of treating various diseases.

  Web site: http://www.delphion.com/details?pn=US06713252__

- **Methods for the simultaneous detection of HCV antigens and HCV antibodies**

  Inventor(s): Dawson; George (Libertyville, IL), Desai; Suresh (Libertyville, IL), Guetierrez; Robin A. (Gurnee, IL), Jiang; Lily (Mundelein, IL), Leary; Thomas P. (Kenosha, WI), Muerhoff; A. Scott (Kenosha, WI), Shah; Dinesh (Libertyville, IL), Stewart; James L. (Libertyville, IL)

  Assignee(s): Abbott Laboratories (Abbott Park, IL)

  Patent Number: 6,727,092

  Date filed: June 17, 2002

  Excerpt(s): The subject invention relates to methods for the simultaneous detection of **Hepatitis C Virus** (HCV) antigens as well as antibodies produced in response to HCV antigens. Furthermore, the subject invention allows one to detect antigens in the early, acute stage of infection, even prior to the development of antibodies, thereby allowing for early detection of infected blood and blood products, and thus improving the safety of the blood supply. Recent epidemiological studies indicate that HCV infects more than 170 million people worldwide and that, in more than 50% of the cases, the infection is chronic. In the United States, there are approximately 4 million people infected, and 30,000 new infections are estimated to occur annually (NIH Conference, Hepatology Suppl 1:2S (1997)). In addition, HCV is responsible for 8,000-10,000 deaths annually in the United States and is the leading indicator for liver transplantation. The HCV genome is a single-stranded RNA molecule of positive polarity that is approximately 9400-9500

nucleotides in length. The organization of the coding regions resembles that of other flaviviruses [Major et al., Hepatology 25:1527 (1997)] as well as the more recently discovered GB viruses [Muerhoff A S, et al., J Virol 69:5621 (1995)]. The HCV genome possesses a large open reading frame (ORF) encoding a polyprotein precursor of 3010 to 3033 amino acids depending on the particular isolate [Choo et al., Proc Natl Acad Sci USA 88:2451 (1991); Grakoui et al., J Virol 67:1385 (1993)]. HCV structural genes (core and envelope) are encoded near the 5'-end of the genome, followed by the proteases and helicase, the helicase cofactor and the replicase. Noncoding regions (NCR), thought to be important in replication, are found at each end of the genome.

Web site: http://www.delphion.com/details?pn=US06727092__

- **NS5B HVC polymerase inhibitors**

  Inventor(s): Jaen; Juan C. (Burlingame, CA), Powers; Jay P. (Pacifica, CA)

  Assignee(s): Tularik Inc. (So. San Francisco, CA)

  Patent Number: 6,727,267

  Date filed: April 5, 2001

  Abstract: Compounds, compositions and methods are provided that are useful in the treatment and prevention of certain viral infections and associated diseases. In particular, the compounds of the invention inhibit the activity of a viral RNA polymerase. The subject methods are particularly useful in the treatment of diseases causes by **hepatitis C virus** infection.

  Excerpt(s): Hepatitis C virus (HCV) is considered to be the major etiological agent of non-A non-B (NANB) hepatitis, chronic liver disease, and hepatocellular carcinoma (HCC) around the world. The viral infection accounts for greater than 90% of transfusion-associated hepatitis in the U.S. and it is the predominant form of hepatitis in adults over 40 years of age. Almost all of the infections result in chronic hepatitis and nearly 20% of infected patients develop liver cirrhosis. The virus particle has not been identified due to the lack of an efficient in vitro replication system and the extremely low amount of HCV particles in infected liver tissues or blood. However, molecular cloning of the viral genome has been accomplished by isolating the messenger RNA (mRNA) from the serum of infected chimpanzees then cloning using recombinant methodologies. See, Grakoui et al. (1993) J. Virol. 67:1385-1395. It is now known that HCV contains a positive strand RNA genome comprising approximately 9400 nucleotides, whose organization is similar to that of flaviviruses and pestiviruses. The genome of HCV, like that of flavi- and pestiviruses, encodes a single large polyprotein of about 3000 amino acids which undergoes proteolysis to form mature viral proteins in infected cells. Cell-free translation of the viral polyprotein and cell culture expression studies have established that the HCV polyprotein is processed by cellular and viral proteases to produce the putative structural and nonstructural (NS) proteins. At least nine mature viral proteins are produced from the polyprotein by specific proteolysis. The order and nomenclature of the cleavage products are as follows: NH.sub.2 -C-E1-E2-NS2-NS3-NS4A-NS4B-NS5A-NS5B-COOH. The three amino terminal putative structural proteins, C (capsid), E1, and E2 (two envelope glycoproteins), are believed to be cleaved by host signal peptidases of the endoplasmic reticulum (ER). The host enzyme is also responsible for generating the amino terminus of NS2. The proteolytic processing of the nonstructural proteins is carried out by the viral proteases: NS2-3 and NS3, contained within the viral polyprotein.

Web site: http://www.delphion.com/details?pn=US06727267__

- **Nucleoside derivatives as inhibitors of RNA-dependent RNA viral polymerase of hepatitis C virus**

  Inventor(s): Bhat; Balkrishen (Carlsbad, CA), Bhat; Neelima (Carlsbad, CA), Carroll; Steven S. (Yardley, PA), Cook; Phillip Dan (Fallbrook, CA), Eldrup; Anne B. (Encinitas, CA), Maccoss; Malcolm (Freehold, NJ), Olsen; David B. (Lansdale, PA), Prakash; Thazha P. (Carlsbad, CA), Prhavc; Marija (Carlsbad, CA), Song; Quanlai (San Marcos, CA)

  Assignee(s): Isis Pharmaceuticals, Inc. (Carlsbad, CA), Merck & Co., Inc. (Rahway, NJ)

  Patent Number: 6,777,395

  Date filed: January 18, 2002

  Excerpt(s): The present invention provides nucleoside compounds and certain derivatives thereof which are inhibitors of RNA-dependent RNA viral polymerase. These compounds are inhibitors of RNA-dependent RNA viral replication and are useful for the treatment of RNA-dependent RNA viral infection. They are particularly useful as inhibitors of **hepatitis C virus** (HCV) NS5B polymerase, as inhibitors of HCV replication, and for the treatment of hepatitis C infection. Hepatitis C virus (HCV) infection is a major health problem that leads to chronic liver disease, such as cirrhosis and hepatocellular carcinoma, in a substantial number of infected individuals, estimated to be 2-15% of the world's population. There are an estimated 4.5 million infected people in the United States alone, according to the U.S. Center for Disease Control. According to the World Health Organization, there are more than 200 million infected individuals worldwide, with at least 3 to 4 million people being infected each year. Once infected, about 20% of people clear the virus, but the rest harbor HCV the rest of their lives. Ten to twenty percent of chronically infected individuals eventually develop liver-destroying cirrhosis or cancer. The viral disease is transmitted parenterally by contaminated blood and blood products, contaminated needles, or sexually and vertically from infected mothers or carrier mothers to their off-spring. Current treatments for HCV infection, which are restricted to immunotherapy with recombinant interferon-.alpha. alone or in combination with the nucleoside analog ribavirin, are of limited clinical benefit. Moreover, there is no established vaccine for HCV. Consequently, there is an urgent need for improved therapeutic agents that effectively combat chronic HCV infection. The state of the art in the treatment of HCV infection has been reviewed, and reference is made to the following publications: B. Dymock, et al., "Novel approaches to the treatment of **hepatitis C virus** infection," Antiviral Chemistry & Chemotherapy, 11:79-96 (2000); H. Rosen, et al., "Hepatitis C virus: current understanding and prospects for future therapies," Molecular Medicine Today, 5:393-399 (1999); D. Moradpour, et al., "Current and evolving therapies for hepatitis C," European J. Gastroenterol. Hepatol., 11:1189-1202 (1999); R. Bartenschlager, "Candidate Targets for Hepatitis C Virus-Specific Antiviral Therapy," Intervirology, 40:378-393 (1997); G. M. Lauer and B. D. Walker, "Hepatitis C Virus Infection," N. Engl. J. Med., 345:41-52 (2001); B. W. Dymock, "Emerging therapies for **hepatitis C virus** infection," Emerging Drugs, 6:13-42 (2001); and C. Crabb, "Hard-Won Advances Spark Excitement about Hepatitis C," Science: 506-507 (2001); the contents of all of which are incorporated by reference herein in their entirety. Different approaches to HCV therapy have been taken, which include the inhibition of viral serine proteinase (NS3 protease), helicase, and RNA-dependent RNA polymerase (NS5B), and the development of a vaccine.

  Web site: http://www.delphion.com/details?pn=US06777395__

- **Nucleotide and deduced amino acid sequences of the envelope 1 gene of 51 isolates of hepatitis C virus and the use of reagents derived from these sequences in diagnostic methods and vaccines**

  Inventor(s): Bukh; Jens (Bethesda, MD), Miller; Roger H. (Rockville, MD), Purcell; Robert H. (Boyds, MD)

  Assignee(s): The United States of America as represented by the Department of Health and (Washington, DC)

  Patent Number: 6,572,864

  Date filed: June 6, 1995

  Abstract: The nucleotide and deduced amino acid sequences of 51 cDNAs are disclosed where each cDNA encodes the envelope 1 gene of an isolate of **hepatitis C virus** (HCV). The invention relates to the oligonucleotides, peptides and recombinant envelope 1 proteins derived from these sequences and their use in diagnostic methods and vaccines.

  Excerpt(s): The present invention is in the field of hepatitis virology. The invention relates to the complete nucleotide and deduced amino acid sequences of the envelope 1 (E1) gene of 51 **hepatitis C virus** (HCV) isolates from around the world and the grouping of these isolates into twelve distinct HCV genotypes. More specifically, this invention relates to oligonucleotides, peptides and recombinant proteins derived from the envelope 1 gene sequences of the 51 isolates of **hepatitis C virus** and to diagnostic methods and vaccines which employ these reagents. Hepatitis C, originally called non-A, non-B hepatitis, was first described in 1975 as a disease serologically distinct from hepatitis A and hepatitis B (Feinstone, S. M. et al. (1975) N. Engl. J. Med. 292:767-770). Although hepatitis C was (and is) the leading type of transfusion-associated hepatitis as well as an important part of community-acquired hepatitis, little progress was made in understanding the disease until the recent identification of **hepatitis C virus** (HCV) as the causative agent of hepatitis C via the cloning and sequencing of the HCV genome (Choo, A. L. et al. (1989) Science 288:359-362). The sequence information generated by this study resulted in the characterization of HCV as a small, enveloped, positive-stranded RNA virus and led to the demonstration that HCV is a major cause of both acute and chronic hepatitis worldwide (Weiner, A. J. et al. (1990) Lancet 335:1-3). These observations, combined with studies showing that over 50% of acute cases of hepatitis C progress to chronicity with 20% of these resulting in cirrhosis and an undetermined proportion progressing to liver cancer, have led to tremendous efforts by investigators within the hepatitis C field to develop diagnostic assays and vaccines which can detect and prevent hepatitis C infection. The cloning and sequencing of the HCV genome by Choo et al. (1989) has permitted the development of serologic tests which can detect HCV or antibody to HCV (Kuo, G. et al. (1989) Science 244:362-364). In addition, the work of Choo et al. has also allowed the development of methods for detecting HCV infection via amplification of HCV RNA sequences by reverse transcription and cDNA polymerase chain reaction (RT-PCR) using primers derived from the HCV genomic sequence (Weiner, A. J. et al.). However, although the development of these diagnostic methods has resulted in improved diagnosis of HCV infection, only approximately 60% of cases of hepatitis C are associated with a factor identified as contributing to transmission of HCV (Alter, M. J. et al. (1989) JAMA 262:1201-1205). This observation suggests that effective control of hepatitis C transmission is likely to occur only via universal pediatric vaccination as has been initiated recently for hepatitis B virus. Unfortunately, attempts to date to protect chimpanzees from hepatitis C infection via

administration of recombinant vaccines have had only limited success. Moreover, the apparent genetic heterogeneity of HCV, as indicated by the recent assignment of all available HCV isolates to one of four genotypes, I-IV (Okamoto, H. et al. (1992) J. Gen. Virol; 73:673-679), presents additional hurdles which must be overcome in order to develop accurate and effective diagnostic assays and vaccines.

Web site: http://www.delphion.com/details?pn=US06572864__

- **Oligonucleotide for highly sensitive detection of hepatitis C virus and method for detection thereof**

  Inventor(s): Ishiguro; Takahiko (Kanagawa, JP), Saito; Juichi (Kanagawa, JP), Taya; Toshiki (Kanagawa, JP)

  Assignee(s): Tosoh Corporation (Yamaguchi, JP)

  Patent Number: 6,756,198

  Date filed: October 29, 2001

  Abstract: An oligonucleotide useful for specific amplification of HCV RNA, or highly sensitive detection and identification of HCV RNA, and a combination thereof. A detection method using RNA amplification step, wherein the oligonucleotide of SEQ ID NO: 11 is used as a first primer and the oligonucleotide of SEQ ID NO: 6 or 7 as a second primer, the oligonucleotide of SEQ ID NO: 12 is used as a first primer and the oligonucleotide of SEQ ID NO: 7 as a second primer, or the oligonucleotide of SEQ ID NO: 13 is used as a first primer and the oligonucleotide of SEQ ID NO: 9 as a second primer.

  Excerpt(s): The present invention relates to an oligonucleotide effective in detecting **Hepatitis C virus** (hereinafter, referred to as "HCV") at clinical laboratory tests and diagnoses, and to a method for detecting HCV using the oligonucleotide. As a method for determining whether the abnormality of liver function is due to HCV or not, an antibody test (enzymatic immunoadsorption method) is known. However, in such a method for detecting anti-HCV antibody, it is impossible to diagnose in its early stages before the antibody is produced. Thus, more highly effective test method is desired at actual clinical site. As described above, in antibody test, it is impossible to diagnose in its early stages of the infection, a complex operation and a long period of time are required, and also it is difficult to detect a very small amount of HCV present in a sample for a short period of time, so that it is desired to develop more rapid and highly sensitive detection method. Furthermore, in order to test more conveniently, it is required to develop an automated test apparatus.

  Web site: http://www.delphion.com/details?pn=US06756198__

- **Oligonucleotide primers for efficient detection of hepatitis C virus (HCV) and methods of use thereof**

  Inventor(s): Gorman; Kevin M. (Penfield, NY), Linnen; Jeffrey M. (San Diego, CA)

  Assignee(s): Ortho-Clinical Diagnostics, Inc. (Raritan, NJ)

  Patent Number: 6,638,714

  Date filed: January 28, 2000

Abstract: Described herein are methods and kits for the detection of **hepatitis C virus** RNA is biological samples obtained from human subjects. The invention includes novel amplification primers and probes useful in the amplification of DNA derived from **hepatitis C virus** RNA, and kits and methods which incorporate the novel primers.

Excerpt(s): The present invention pertains to improved methods for detecting nucleic acid sequences in biological samples, particularly sequences derived from infectious microorganisms. Hepatitis C Virus (HCV) is a parenterally transmitted virus responsible for the majority of cases of post-transfusion hepatitis and a substantial portion of sporadic (or community acquired) hepatitis cases worldwide. It is estimated that more than 1% of the world's population is infected with HCV. HCV infection is associated with acute hepatitis, chronic hepatitis, cirrhosis, and hepatocellular carcinoma. Analysis of HCV coding sequences from around the world has revealed considerable sequence variation among individual viral isolates. Furthermore, analyses of HCV sequences from individual patients have shown that the virus circulates as so-called "quasi-species," which contain related but not identical sequences. The variation that exists among isolates and within individual patients is believed to be the result of the low fidelity of the virally-encoded RNA-dependent RNA polymerase. The degree of genetic variability of HCV has important implications for prevention, diagnosis, and control of infection.

Web site: http://www.delphion.com/details?pn=US06638714__

- **Protein fragments for use in protein targeting**

  Inventor(s): Hope; Ralph Graham (Glasgow, GB), McLauchlan; John (Glasgow, GB)

  Assignee(s): Medical Research Council (London, GB)

  Patent Number: 6,670,462

  Date filed: October 1, 2001

  Abstract: A protein is described. The protein comprises a lipid globule targeting sequence linked to a protein of interest (POI) wherein the targeting sequence comprises a **hepatitis C virus** (HCV) core protein or fragment or homologue thereof.

  Excerpt(s): This invention relates to the use of polypeptides derivable from the core protein of the **hepatitis C virus** for targeting proteins of interest to lipid globules, in particular lipid globules subsequently secreted into animal milk. The resulting protein/lipid complexes may be used in therapy including the production of vaccines. Hepatitis C virus (HCV) is a major causative agent of chronic hepatitis and liver disease. It is estimated that, worldwide, approximately 300 million individuals are infected with the virus, 20% of whom are likely to develop mild to severe liver disease or carcinoma. Apart from the risk of succumbing to the long term effects of infection, these individuals also represent a large reservoir of virus for future transmissions. To date, the only widely used therapy for HCV is treatment with interferon. However, sustained response is achieved in only about 20% of cases. Moreover, no vaccine currently exists to protect against infection. Since growth of the virus has not been possible to date in tissue culture systems, very little is known also about the molecular events which occur during viral replication. The core protein of HCV is predicted to constitute the capsid of virus particles. From various studies, expression of this protein results in a range of effects on intracellular processes, including a decrease in transcription of genes from HBV and HIV and alterations to apoptosis. There is also evidence from a study on transgenic mice that liver-specific expression of core may be linked to the development of steatosis (fatty liver), a condition commonly found in HCV-infected individuals which is characterized

by the accumulation of fat deposits within hepatocytes. Thus, core protein may also influence lipid metabolism within the liver. Other results from studies on human sera suggest that HCV virus particles are found associated with lipoprotein particles which are produced by the liver. It has also been shown that HCV core protein associates with lipid droplets within cells (Barba, G. et al., 1997; Moradpour, D. et al., 1996). The droplets are storage compartments for both triacylglycerols and cholesterol esters which can be used as substrates for oxidation in mitochondria and for the formation of membranes. In specialized cells, stored cholesterol is used for steroid hormone synthesis.

Web site: http://www.delphion.com/details?pn=US06670462__

- **Reporter gene system for use in cell-based assessment of inhibitors of the hepatitis C virus protease**

  Inventor(s): Jackson; Roberta Lynn (San Diego, CA), Patick; Amy Karen (Escondido, CA), Potts; Karen Elizabeth (Solana Beach, CA)

  Assignee(s): Agouron Pharmaceuticals, Inc. (San Diego, CA)

  Patent Number: 6,599,738

  Date filed: August 2, 2001

  Abstract: A cell-based assay system in which the detection of the reporter gene activity, or secreted alkaline phosphatase (SEAP), is dependent upon the protease activity of the **Hepatitis C virus** NS3 gene product. This system can be used to assess the activity of candidate protease inhibitors in a mammalian cell-based assay system. The assay system is simpler than previously described assays due to the use of SEAP which allows the reporter gene activity to be quantified by measuring the amount of secreted gene product in the cell media by monitoring the conversion of luminescent or colorimetric alkaline phosphatase substrate.

  Excerpt(s): A cell-based assay system in which the detection of reporter gene activity (secreted alkaline phosphatase or SEAP) is dependent upon active **Hepatitis C virus** (HCV) NS3 protease. The assay system is useful in the in vitro screening, in a mammalian cell-based assay, of potential protease inhibiting molecules useful in the treatment of HCV. The advantages of using SEAP over more routinely used reporter genes such as beta-galactosidase or luciferase, is that a cell lysis step is not required since the SEAP protein is secreted out of the cell. The absence of a cell lysis step decreases intra- and inter-assay variability as well as makes the assay easier to perform then earlier assays. The NS2/3 is a metalloprotease and has been shown to mediate cleavage at the 2/3 junction site Grakoui, et al. (1993); Hijikata, M., et al., J. Virol. 67:4665-4675 1993. In contrast, the NS3 protease is required for multiple cleavages within the nonstructural segment of the polyprotein, specifically the 3/4A, 4A/4B, 4B/5A, and 5A/5B junction sites Bartenschlager et al. (1993); Eckart, M. R., et al., Biochem. Biophys. Res. Comm. 192:399-406 1993; Grakoui et al. (1993); Tomei et al. (1994). More recently, it is thought that the NS2/3 protease might actually be part of the HCV NS3 protease complex even though they have two functionally distinct activities. Although NS3 protease is presumed to be essential for HCV viability, definitive proof of its necessity has been hampered by the lack of an infectious molecular clone that can be used in cell-based experiments. However, recently two independent HCV infectious molecular clones have been developed and have been shown to replicate in chimpanzees. Kolykhalov, A. A., et al., Science 277:570-574 1997; Yanagi, M., et al., Proc. Natl. Acad. Sci. 94:8738-8743 1997. The requirement for NS3 in the HCV life cycle may

be validated in these clones by using oligo nucleotide-mediated site directed mutagenesis to inactivate the NS3 catalytic serine residue and then determining whether infectious virus is produced in chimpanzees. Until these experiments are performed, the necessity of NS3 is inferred from cell-based experiments using the related yellow fever (YFV) and bovine viral diarrhea (BVDV) viruses. Mutagenesis of the YFV and BVDV NS3 protease homologs has shown that NS3 serine protease activity is essential for YFV and BVDV replication. Chambers, T. J., et al., Proc. Natl. Acad. Sci. 87:8898-8902 1990; Xu, J., et al., J. Virol. 71:5312-5322 1997. In general, when investigators screen potential anti-viral compounds for inhibitory activity, it usually involves initial in vitro testing of putative enzyme inhibitors followed by testing the compounds on actual infected cell lines and animals. It is obvious that working with live virus in large scale screening activities can be inherently dangerous and problematic. While final testing of putative inhibitors in infected cells and animals is still necessary for preclinical drug development, for initial screening of candidate molecules, such work is cost-prohibitive and unnecessary. Furthermore, the inability to grow HCV in tissue culture in a reproducible quantitative manner prevents the evaluation of potential antiviral agents for HCV in a standard antiviral cytopathic effect assay. In response to this real need in the industry, development of non-infectious, cell-based, screening systems is essential.

Web site: http://www.delphion.com/details?pn=US06599738__

- **Single-chain recombinant complexes of hepatitis C virus NS3 protease and NS4A cofactor peptide**

  Inventor(s): Malcolm; Bruce A. (Westfield, NJ), Taremi; S. Shane (Upper Montclair, NJ), Weber; Patricia C. (Yardley, PA), Yao; Nanhua (Irvine, CA)

  Assignee(s): Schering Corporation (Kenilworth, NJ)

  Patent Number: 6,653,127

  Date filed: October 6, 2000

  Abstract: Covalent HCV NS4A-NS3 complexes comprising the central hydrophobic domain of native HCV NS4A peptide, a linker, and the HCV NS3 serine protease domain, wherein the hydrophobic domain of native HCV NS4A peptide is tethered by the linker to the amino terminus of the HCV NS3 protease domain.

  Excerpt(s): Hepatitis C virus (HCV) is considered to be the major etiological agent of non-A non-B (NANB) hepatitis, chronic liver disease, and hepatocellular carcinoma (HCC) around the world, with an estimated human seroprevalence of 1% globally. [Alter et al., 1994, Gastroenterol. Clin. North Am. 23:437-455; Behrens et al., 1996, EMBO J. 15:12-22]. Four million individuals may be infected in the United States. The viral infection accounts for greater than 90% of transfusion-associated hepatitis in the U.S. and it is the predominant form of hepatitis in adults over 40 years of age. Almost all of the infections result in chronic hepatitis and nearly 20% of those infected develop liver cirrhosis. The virus particle has not been identified due to the lack of an efficient ex vivo replication system and the extremely low amount of HCV particles in infected liver tissues or blood. However, molecular cloning of the viral genome has been accomplished by isolating the messenger RNA (mRNA) from the serum of infected chimpanzees and preparing cDNA using recombinant methodologies. [Grakoui A. et al., 1993, J. Virol. 67: 1385-1395]. It is now known that HCV contains a positive strand RNA genome comprising approximately 9400 nucleotides, organization of which is similar to that of flaviviruses and pestiviruses. The genome of HCV, a (+)-stranded RNA molecule of.about.9.4 kb, encodes a single large polyprotein of about 3000 amino acids which

undergoes proteolysis to form mature viral proteins in infected cells. The NS3 protease catalyzes the rest of the cleavages in the nonstructural part of the polyprotein. The NS3 protein contains 631 amino acid residues and is comprised of two enzymatic activities: the protease domain contained within amino acid residues 1-181 and a helicase ATPase domain contained within the rest of the protein Kim et al., 1995, Biochem Biophys Res. Comm., 215:160-166. It is not known if the 70 kD NS3 protein is cleaved further in infected cells to separate the protease domain from the helicase domain, although no cleavage has been observed in cell culture expression studies.

Web site: http://www.delphion.com/details?pn=US06653127__

- **Target-dependent reactions using structure-bridging oligonucleotides**

  Inventor(s): Anderson; Todd A. (Madison, WI), Brow; Mary Ann D. (Madison, WI), Dahlberg; James E. (Madison, WI), Dong; Fang (Madison, WI), Fors; Lance (Madison, WI), Lyamichev; Victor I. (Madison, WI), Neri; Bruce P. (Madison, WI), Prudent; James R. (Madison, WI)

  Assignee(s): Third Wave Technologies, Inc. (Madison, WI)

  Patent Number: 6,709,815

  Date filed: July 18, 2000

  Abstract: The present invention relates to methods and compns. for treating nucleic acids, and in particular, methods and compns. for the detection and characterization of nucleic acid sequences and sequence changes. The invention provides methods for examg. the conformations assumed by single strands of nucleic acid, forming the basis of novel methods of detection of specific nucleic acid sequences. The present invention contemplates use of novel detection methods for, among other uses, clinical diagnostic purposes, including but not limited to the detection and identification of pathogenic organisms. Examples are presented for the analysis of Mycobacterium tuberculosis and **hepatitis C virus** genes.

  Excerpt(s): The present invention relates to methods and compositions for analyzing nucleic acids, and in particular, methods and compositions for detection and characterization of nucleic acid sequences and sequence changes. The detection and characterization of specific nucleic acid sequences and sequence changes have been utilized to detect the presence of viral or bacterial nucleic acid sequences indicative of an infection, the presence of variants or alleles of mammalian genes associated with disease and cancers, and the identification of the source of nucleic acids found in forensic samples, as well as in paternity determinations. As nucleic acid sequence data for genes from humans and pathogenic organisms accumulates, the demand for fast, cost-effective, and easy-to-use tests for as yet unknown, as well as known, mutations within specific sequences is rapidly increasing. A handful of methods have been devised to scan nucleic acid segments for mutations. One option is to determine the entire gene sequence of each test sample (e.g., a clinical sample suspected of containing bacterial strain). For sequences under approximately 600 nucleotides, this may be accomplished using amplified material (e.g., PCR reaction products). This avoids the time and expense associated with cloning the segment of interest. However, specialized equipment and highly trained personnel are required for DNA sequencing, and the method is too labor-intense and expensive to be practical and effective in the clinical setting.

  Web site: http://www.delphion.com/details?pn=US06709815__

- **Treatment of hepatitis C virus infections with interleukin-10**

  Inventor(s): Davis; Gary L. (Gainesville, FL), Grint; Paul C. (San Diego, CA), Nelson; David R. (Gainesville, FL)

  Assignee(s): Schering Corporation (Kenilworth, NJ)

  Patent Number: 6,685,931

  Date filed: December 20, 1999

  Abstract: The hepatoprotective effect of IL-10 is described, in particular, the use of interleukin-10 in the treatment of liver damage (e.g. fibrosis or cirrhosis) in a difficult-to-treat patient afflicted with chronic **hepatitis C virus** infection who has failed to respond to, or achieve a sustained virologic response to an anti-HCV therapy(e.g., interferon-.alpha. in combination with ribavirin).

  Excerpt(s): The invention is directed to the use of interleukin-10 to improve liver histology in patients afflicted with chronic **hepatitis C virus** infections. In particular, the invention relates to the use of interleukin-10 to reduce hepatic fibrosis in difficult-to-treat patients afflicted with chronic **hepatitis C virus** infections. Chronic hepatitis C is an insidious and slowly progressive disease having a significant impact on morbidity and mortality. While many patients who contract hepatitis C will have subclinical or mild disease, HCV infection causes progressive liver damage in the majority of those infected. At least 80% of the individuals who contract HCV will develop chronic infection and hepatitis, a disease state characterized by fluctuating serum transaminase abnormalities and inflammatory with or without fibrosis lesions on liver biopsy. Twenty to fifty percent of these will eventually progress to cirrhosis and 1-2% will develop liver cancer after a 10-20 year period. Multiple factors influence the hepatitis C virus-host interaction resulting in a unique individual disease pattern. In individuals chronically infected with HCV, there is persistent viremia and liver damage despite the presence of both humoral and cellular responses. The mechanisms responsible for hepatocellular injury are not fully understood. The role of IL-10 in inhibiting liver fibrogenesis has been evaluated in the mouse. Two studies (Louis et al., Heptatology, 1998;28:1607-1615; and Thompson et al., Heptatology, 1998;28:1597-1606) showed that IL-10 knock-out mice develop significantly more severe fibrosis than wild-type mice.

  Web site: http://www.delphion.com/details?pn=US06685931__

Patent Applications on Hepatitis C Virus

As of December 2000, U.S. patent applications are open to public viewing.[9] Applications are patent requests which have yet to be granted. (The process to achieve a patent can take several years.) The following patent applications have been filed since December 2000 relating to hepatitis C virus:

[9] This has been a common practice outside the United States prior to December 2000.

- **2', 3'-Dideoxynucleoside analogues for the treatment or prevention of Flaviviridae infections**

  Inventor(s): Schinazi, Raymond F.; (Decatur, GA), Shi, Junxing; (Duluth, GA), Striker, Robert; (Madison, WI)

  Correspondence: King & Spalding; 191 Peachtree Street, N.E.; Atlanta; GA; 30303-1763; US

  Patent Application Number: 20040067877

  Date filed: August 1, 2003

  Abstract: A method for the treatment or prevention of Flaviviridae infections, in particular, **hepatitis C virus** infection, in a host, and in particular, a human, is provided that includes administering an effective amount of a.beta.-L- or.beta.-D-2',3'-dideoxynucleoside or a pharmaceutically acceptable salt or prodrug thereof, optionally in a pharmaceutically acceptable diluent or excipient.

  Excerpt(s): This application claims priority to U.S. Provisional Application No. 60/453,715, filed on Aug. 1, 2002, the disclosure of which is incorporated herein. The present invention is a method for the treatment or prevention of Flaviviridae infections using nucleoside analogues. More specifically, the invention describes 2',3'-dideoxynucleoside analogues, pharmaceutically acceptable salts or other derivatives thereof, and the use thereof in the treatment of a Flaviviridae viral infection, and, in particular, a **hepatitis C virus** (HCV) infection. Flaviviridae are a group of positive, single-stranded RNA viruses with genome sizes from 9 to 15 kb. They are enveloped viruses of approximately 40-50 nm. An overview of the Flaviviridae taxonomy is available from the International Committee for Taxonomy of Viruses. The group Flaviviridae consists of three genera.

  Web site: http://appft1.uspto.gov/netahtml/PTO/search-bool.html

- **Anti-HCV nucleoside derivatives**

  Inventor(s): Devos, Rene; (Welwyn Garden City, GB), Dymock, Brian William; (St. Albans, GB), Hobbs, Christopher John; (Hertford, GB), Jiang, Wen-Rong; (Welwyn Garden City, GB), Martin, Joseph Armstrong; (Harpenden, GB), Merrett, John Herbert; (Baldock, GB), Najera, Isabel; (St. Albans, GB), Shimma, Nobuo; (Chigasaki-shi, JP), Tsukuda, Takuo; (Odawara-shi, JP)

  Correspondence: Hoffmann-La Roche INC.; Patent Law Department; 340 Kingsland Street; Nutley; NJ; 07110

  Patent Application Number: 20040110718

  Date filed: October 3, 2003

  Abstract: The present invention comprises novel and known purine and pyrimidine nucleoside derivatives which have been discovered to be active against **hepatitis C virus** (HCV). The use of these derivatives for the treatment of HCV infection is claimed as are the novel nucleoside derivatives disclosed herein.

  Excerpt(s): This application is a Continuation of Ser. No. 09/923,620, filed Aug. 7, 2001, which is now pending. Hepatitis C virus is the leading cause of chronic liver disease throughout the world. Patients infected with HCV are at risk of developing cirrhosis of the liver and subsequent hepatocellular carcinoma and hence HCV is the major indication for liver transplantation. Only two approved therapies are currently available

for the treatment of HCV infection (R. G. Gish, Sem. Liver. Dis., 1999, 19, 35). These are interferon-.alpha. monotherapy and, more recently, combination therapy of the nucleoside analogue, ribavirin (Virazole), with interferon-.alpha. (IMPDH) (D. G. Streeter et al, Proc. Natl. Acad. Sci., 1973, 70,1174) and direct inhibition of viral DNA or RNA replication (R. W. Sidwell et al, Science, 177,705).

Web site: http://appft1.uspto.gov/netahtml/PTO/search-bool.html

- **Anti-idiotypic antibody and its use in diagnosis and therapy of hepatitis c virus related diseases**

  Inventor(s): Grant, Michael D.; (St Johns, CA)

  Correspondence: Townsend And Townsend And Crew, Llp; Two Embarcadero Center; Eighth Floor; San Francisco; CA; 94111-3834; US

  Patent Application Number: 20040146857

  Date filed: March 11, 2004

  Abstract: The present invention provides methods for the diagnosis, prognosis and treatment of HCV-related disease. The method takes advantage of a novel reactive mechanism of the murine monoclonal antibody (mAb) 1F7 against human antibodies specific for different proteins of the **Hepatitis C Virus** (HCV) and Human immunodeficiency virus (HIV). 1F7 recognizes antibodies against HCV core protein in a majority of HCV-infected individuals and antibodies against HCV non-structural proteins 3 (NS3) and NS4 in some HCV-infected individuals. 1F7 also recognizes antibodies against the putative principle neutralizing determinant (hypervariable and conserved region 1 of the HCV E2 protein) of HCV. The antibody can be used in various methods to detect HCV related disease and formulated with physiologically acceptable carriers in various compositions to treat HCV infection.

  Excerpt(s): The present invention provides methods and compositions for the diagnosis, monitoring, and modulation of the immune response to **Hepatitis C Virus** (HCV) related diseases. The methods take advantage of a novel reactive mechanism of the murine monoclonal antibody (mAb) 1F7 against human antibodies specific for different proteins of the **Hepatitis C virus** (HCV). In particular, the antibodies recognize HCV core protein in a majority of HCV-infected individuals and antibodies against HCV non-structural proteins 3 (NS3) and NS4 in some HCV-infected individuals. Also, the antiidiotypic antibody recognizes antibodies against the putative principle neutralizing determinant (hypervariable region 1 of the HCV E2 protein) of HCV. The idiotypic linking of antibodies against multiple epitopes of a chronic pathogen provides methods for improved diagnosis and monitoring of HCV as well as opportunities to increase the efficiency of immune regulation, including limiting "idiotypic "grid-lock", that can arise from chronic antigenic stimulation. Hepatitis C virus)HCV) is a plus sence RNA virus that establishes chronic infection in up to 80% of exposed individuals. Long-term infection can lead to liver cirrhosis and hepatocellular carcinoma Currently, no effective vaccine or treatment for HCV infection is available. The ability of HCV to mutate key immunological determinants and to escape immune selection pressures exerted by antibodies and T cells in an infected individual is important for the establishment of chronic infection. Similar to HIV infection, the immune system can become locked into recognition of the original infecting strain of HCV and therefore is unable to adapt to, and recognize, subsequent mutations. Antibodies against a particular region of HCV E2 protein, hypervariable region 1 (HVR1) are believed to be important to preventing new infection of cells and promoting clearance of vira particles. An antibody response

directed against a broad range of HCV epitopes in addition to HCV E2 HVR1 would be expected to provide better protection against HCV mutants and to be associated with a more favorable clinical outcome to infection. Although HCV and HIV are genetically unrelated and the viruses have a different pattern of cellular tropism and induce distinct diseases, HCV and HIV share important features relevant to their interactions with the immune system of the infected host. In particular, both viruses commonly establish chronic infections, thought at least in part, to be due to RNA polymerases characterized as "mistake-prone" that generate a high mutation rate during viral replication (Bebenek et al., J. Biol. Chem. 264:16948-16956 (1989); Ogata et al., Proc. Natl. Acad. Sci USA 88:3392-3396 (1991). These mutations produce viral variants which can undergo immune selective pressures in the infected host. The selective pressures favor the outgrowth of those viral variants poorly neutralized by the anti-viral antibodies concurrently present in the host. Therefore, the less diverse the neutralizing response to the infecting virus, the more easily viral escape occurs through random mutations within neutralization epitopes. Since random mutations cannot be anticipated by the immune system, adaptation of the immune response lags behind the virus resulting in chronic infection.

Web site: http://appft1.uspto.gov/netahtml/PTO/search-bool.html

- **Antiviral compounds**

  Inventor(s): Taylor, Debra Lynn; (London, GB), Tyms, Albert Stanley; (London, GB)

  Correspondence: Ohlandt, Greeley, Ruggiero & Perle, Llp; One Landmark Square, 10th Floor; Stamford; CT; 06901; US

  Patent Application Number: 20040147549

  Date filed: March 9, 2004

  Abstract: Use of certain castanospermine esters in the treatment of diseases caused by flaviviruses, in particular in the tretment of disease caused by the **hepatitis C virus** (HCV) and compositions containing said esters in combination with adjunctive therapeutic agents.

  Excerpt(s): The present invention relates to the use of certain castanospermine esters in the treatment of diseases caused by flaviviruses, in particular in the treatment of disease caused by the **hepatitis C virus** (HCV). The flavivirus group (family Flaviviridae) comprises the genera Flavivirus, Pestivirus and Hepacivirus and includes the causative agents of numerous human diseases and a variety of animal dieases which cause significant losses to the livestock industry. The family Flavivirdae (members of which are referred to herein as flaviviruses) include the genera Flavivirus (e.g. yellow fever virus, dengue viruses, Japanese encephalitis virus and tick-borne encephalitis virus), Pestivirus (e.g. bovine viral diarrhoea virus, classical swine fever virus and border disease virus), Hepacivirus (**hepatitis C virus**) and currently unclassified members of the Flaviviridae (e.g. GB virus types A, B and C).

  Web site: http://appft1.uspto.gov/netahtml/PTO/search-bool.html

- **Antiviral nucleoside derivatives**

  Inventor(s): Martin, Joseph Armstrong; (Menlo Park, CA), Sarma, Keshab; (Sunnyvale, CA), Smith, David Bernard; (San Mateo, CA), Smith, Mark; (San Francisco, CA)

  Correspondence: Roche Palo Alto Llc; Patent Law DEPT. M/s A2-250; 3431 Hillview Avenue; Palo Alto; CA; 94304; US

  Patent Application Number: 20040121980

  Date filed: November 19, 2003

  Abstract: The present invention relates to nucleoside derivatives for the treatment of Hepatitis C viral infections including compounds of formula I, pharmaceutical compositions comprising these compounds and methods for treatment or prophylaxis of **Hepatitis C Virus** mediated diseases employing said compounds in monotherapy or in combination therapy. The present invention further provides a process for preparing 1',3',4'-triacyl pyrimidine nucleoside from a N, 1',3',4'-tetraacylpyrimidine nucleoside 1

  Excerpt(s): This application claims benefit under Title 35 U.S.C. 119(e) of U.S. Provisional Application No. 60/427,447, filed Nov. 19, 2002 and U.S. Pat. No. 60/483,970, filed Jul. 1, 2003, which are hereby incorporated by reference in their entirety. The invention relates to the field of antiviral therapy and in particular to nucleoside derivatives for treating **Hepatitis C Virus** (HCV) mediated diseases. The invention provides novel chemical compounds, pharmaceutical compositions comprising these compounds, methods for treatment or prophylaxis of HCV mediated diseases employing said compounds in monotherapy or in combination therapy. The invention relates to nucleoside derivatives as inhibitors of HCV replicon RNA replication. In particular, the invention is concerned with the use of pyrimidine nucleoside compounds as inhibitors of subgenomic HCV RNA replication and pharmaceutical compositions containing such compounds.

  Web site: http://appft1.uspto.gov/netahtml/PTO/search-bool.html

- **Compositions and mehtods for treatment of Hepatitis C virus-associated diseases**

  Inventor(s): Anderson, Kevin P.; (Carlsbad, CA), Dorr, F. Andrew; (Solana Beach, CA), Hanecak, Ronnie C.; (San Clemente, CA), Kwoh, T. Jesse; (Carlsbad, CA), Nozaki, Chikateru; (Kuamoto-shi, JP)

  Correspondence: Licata & Tyrrell P.C.; 66 East Main Street; Marlton; NJ; 08053; US

  Patent Application Number: 20040049021

  Date filed: June 4, 2003

  Abstract: Antisense oligonucleotides are provided which are complementary to and hybridizable with at least a portion of HCV RNA and which are capable of inhibiting the function of the HCV RNA. These oligonucleotides can be administered to inhibit the activity of **Hepatitis C virus** in vivo or in vitro. These compounds can be used either prophylactically or therapeutically to reduce the severity of diseases associated with **Hepatitis C virus,** and for diagnosis and detection of HCV and HCV-associated diseases. Methods of using these compounds are also disclosed.

  Excerpt(s): This application is a continuation-in-part of U.S. Ser. No. 09/853,409, filed May 11, 2001, which is a continuation-in-part of U.S. Ser. No. 09/690,936 filed Oct. 18, 2000, which is a continuation of U.S. Ser. No. 08/988,321, filed Dec. 10, 1997, now issued as U.S. Pat. No. 6,174,868, which is a continuation-in-part of U.S. Ser. No. 08/650,093,

filed May 17, 1996, now issued as U.S. Pat. No. 6,391,542, which is a continuation-in-part of U.S. Ser. No. 08/452,841 filed May 30, 1995, now issued as U.S. Pat. No. 6,423,489, which in turn is a continuation-in-part of U.S. Ser. No. 08/397,220, filed Mar. 9, 1995, now issued as U.S. Pat. No. 6,284,458, which is the U.S. National Phase filing of PCT/JP93/01293 filed Sep. 10, 1993, which is a continuation-in-part of U.S. Ser. No. 07/945,289, filed Sep. 10, 1992, which is now abandoned. This invention relates to the design and synthesis of antisense oligonucleotides which can be administered to inhibit the activity of **Hepatitis C virus** in vivo or in vitro and to prevent or treat Hepatitis C virus-associated disease. These compounds can be used either prophylactically or therapeutically to reduce the severity of diseases associated with **Hepatitis C virus.** These compounds can also be used for detection of **Hepatitis C virus** and diagnosis of Hepatitis C virus-associated diseases. Oligonucleotides which are specifically hybridizable with **Hepatitis C virus** RNA targets and are capable of inhibiting the function of these RNA targets are disclosed. Methods of using these compounds are also disclosed. The predominant form of hepatitis currently resulting from transfusions is not related to the previously characterized Hepatitis A virus or Hepatitis B virus and has, consequently, been referred to as Non-A, Non-B Hepatitis (NANBH). NANBH currently accounts for over 90% of cases of post-transfusion hepatitis. Estimates of the frequency of NANBH in transfusion recipients range from 5%-13% for those receiving volunteer blood, or 25-54% for those receiving blood from commercial sources.

Web site: http://appft1.uspto.gov/netahtml/PTO/search-bool.html

- **Compounds useful for treating Hepatitis C virus**

  Inventor(s): Decicco, Carl P.; (Kennett Square, PA), Hudyma, Thomas W.; (Durham, CT), Priestley, Eldon Scott; (Hockessin, DE), Zheng, Xiaofan; (Cheshire, CT)

  Correspondence: Stephen B. Davis; Bristol-Myers Squibb Company; Patent Department; P O Box 4000; Princeton; NJ; 08543-4000; US

  Patent Application Number: 20040067976

  Date filed: August 27, 2003

  Abstract: A series of compounds of Formula I are disclosed which are useful in treating viral hepatitus C. 1

  Excerpt(s): This application claims the benefit of U.S. provisional application U.S. S No. 60/324,874, filed Sep. 26, 2001. The present invention is directed to compounds which inhibit the RNA-dependent RNA polymerase (RdRp) encoded by **Hepatitis C virus** (HCV). The compounds, or pharmaceutically acceptable salts or prodrugs thereof, are of value in the treatment and/or prevention of infection by HCV. The Field of the Invention. HCV is a major human pathogen, infecting an estimated 170 million persons worldwide--roughly five times the number infected by human immunodeficiency virus type 1. A substantial fraction of these HCV infected individuals develop serious progressive liver disease, including cirrhosis and hepatocellular carcinoma. (Lauer, G. M.; Walker, B. D. N. Engl. J. Med. (2001), 345, 41-52).

  Web site: http://appft1.uspto.gov/netahtml/PTO/search-bool.html

- **Fused-ring compounds and use thereof as drugs**

  Inventor(s): Hashimoto, Hiromasa; (Takatsuki-shi, JP), Mizutani, Kenji; (Takatsuki-shi, JP), Yoshida, Atsuhito; (Takatsuki-shi, JP)

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  Patent Application Number: 20040097438

  Date filed: July 8, 2003

  Abstract: The present invention provides a fused ring compound of the following formula [I] 1wherein each symbol is as defined in the specification, a pharmaceutically acceptable salt thereof, and a therapeutic agent for hepatitis C, which contains this compound. The compound of the present invention shows an anti-hepatitis C virus (HCV) action based on the HCV polymerase inhibitory activity, and is useful as a therapeutic agent or prophylactic agent for hepatitis C.

  Excerpt(s): This application is a divisional of copending U.S. patent application Ser. No. 09/939,374, filed Aug. 24, 2001, which is a continuation-in-part of PCT/JP00/09181 filed on Dec. 22, 2000. The present invention relates to a novel fused ring compound and a pharmaceutically acceptable salt thereof useful as a therapeutic agent for hepatitis C, and to an intermediate compound for the synthesis thereof. The present invention also relates to a novel use of a certain fused ring compound or a pharmaceutically acceptable salt thereof as a therapeutic agent for hepatitis C. More particularly, the present invention relates to a therapeutic agent for hepatitis C, which contains a novel fused ring compound or a Pharmaceutically acceptable salt thereof, which is effective for the prophylaxis or treatment of hepatitis C and which shows anti-hepatitis C virus (HCV) activity, particularly anti-HCV activity based on an RNA-dependent RNA polymerase inhibitory activity. In 1989, a main causative virus of non-A non-B posttransfusion hepatitis was found and named **hepatitis C virus** (HCV). Since then, several types of hepatitis viruses have been found besides type A, type B and type C, wherein hepatitis caused by HCV is called hepatitis C.

  Web site: http://appft1.uspto.gov/netahtml/PTO/search-bool.html

- **HBV/HCV virus-like particle**

  Inventor(s): Glazer, Edward; (Oakland, CA), Houghton, Michael; (Berkeley, CA), Selby, Mark; (San Francisco, CA)

  Correspondence: Chiron Corporation; Intellectual Property - R440; P.O. Box 8097; Emeryville; CA; 94662-8097; US

  Patent Application Number: 20040146529

  Date filed: November 17, 2003

  Abstract: Chimeric antigens derived from hepatitis B virus (HBV) and **hepatitis C virus** (HCV) are described which form virus-like particles when co-expressed with an excess of hepatitis B virus surface antigen (HBsAg). The chimeric antigens are fusion proteins containing an immunogenic peptide derived from an HCV protein coupled to the amino terminus of HBsAg. Also described are nucleic acid constructs and vectors for transfection of cells and expression of the chimeric antigens. The invention further provides methods for producing HBV/HCV virus-like particles containing the chimeric antigens, cell lines for producing the virus-like particles, combination vaccines

containing the virus-like particles, and DNA vaccines that express the virus-like particles.

Excerpt(s): This application is related to provisional patent application serial No. 60/167,224, filed Nov. 24, 1999, from which priority is claimed under 35 USC.sctn.119(e)(1) and which is incorporated herein by reference in its entirety. The invention is related to the area of recombinant vaccines. It is particularly related to the field of chimeric antigens and virus-like particles for use in vaccines, especially combination vaccines for Hepatitis B virus (HBV) and **Hepatitis C virus** (HCV). Hepatitis C virus (HCV) infects approximately 1% of the world's population and causes serious health problems. Over 75% of acutely infected individuals eventually progress to a chronic carrier state that can result in cirrhosis, liver failure, and hepatocellular carcinoma. A very small fraction of chronically infected patients clear HCV naturally and resolve chronic hepatitis. See Alter et al. (1992) N. Engl. J. Med. 327:1899-1905; Resnick and Koff. (1993) Arch. Intem. Med. 153:1672-1677; Seeff (1995) Gastrointest. Dis. 6:20-27; Tong et al. (1995) N. Engl. J. Med. 332:1463-1466. Immunization against E2 glycoproteins of some flaviviruses (see e.g., Konishi et al., (1992) Virology 188: 714-720), including HCV (Ishii et al., (1998) Hepatology 28: 1117-1120), may protect against infection. However, attempts to express recombinant HCV E1 and E2 glyocoproteins have been frustrated by the fact that these proteins are not secreted from the host cell but are retained within the endoplasmic reticulum (Dubuisson et al. (1994) J. Virology 68: 6147-6160).

Web site: http://appft1.uspto.gov/netahtml/PTO/search-bool.html

- **HCV peptide compositions**

  Inventor(s): Choo, Qui-Lim; (El Cerrito, CA), Houghton, Michael; (Danville, CA), Kuo, George; (San Francisco, CA)

  Correspondence: Banner & Witcoff; 1001 G Street N W; Suite 1100; Washington; DC; 20001; US

  Patent Application Number: 20040091851

  Date filed: November 12, 2002

  Abstract: A family of cDNA sequences derived from **hepatitis C virus** (HCV) are provided. These sequences encode antigens which react immunologically with antibodies present in individuals with non-A non-B hepatitis (NANBV), but which are absent from individuals infected with hepatitis A virus, or hepatitis B virus, and also are absent in control individuals. The HCV cDNA sequences lack substantial homology to the sequences of hepatitis delta virus (HDV) and HBV. A comparison of the sequences of amino acids encoded in the HCV cDNA with the sequences of Flaviviruses indicated that HCV may be related to the Flaviviruses.The HCV cDNA sequences and the polypeptides encoded therein are useful as reagents for the detection and therapy of HCV. The reagents provided in the invention are also useful for the isolation of NANBV agent(s), for the propagation of these agents in tissue culture, and for the screening of antiviral agents for HCV.

  Excerpt(s): The application is a continuation of Ser. No. 08/686,342 filed Jul. 25, 1996, which is a continuation-in-part of Ser. No. 07/355,002 filed May 18, 1989, abandoned, which is a continuation-in-part of Ser. No. 07/341,334 filed Apr. 20, 1989, abandoned, which is a continuation-in-part of Ser. No. 353,896 filed Apr. 21, 1989, abandoned, which is a continuation-in-part of Ser. No. 07/325,338 filed Mar. 17, 1989, abandoned, which is

a continuation-in-part of Ser. No. 271,450 filed Nov. 14, 1988, abandoned, which is a continuation-in-part of Ser. No. 263,584 filed Oct. 26, 1988, abandoned, which is a continuation-in-part of Ser. No. 191,263 filed May 6, 1988, abandoned, which is a continuation-in-part of Ser. No. 161,072 filed Feb. 26, 1988, abandoned, which is a continuation-in-part of Ser. No. 139,886 filed Dec. 30, 1987, abandoned, which is a continuation-in-part of Ser. No. 122,714 filed Nov. 18, 1987, abandoned. These references are incorporated herein by reference in their entireties. The invention relates to materials and methodologies for managing the spread of non-A, non-B hepatitis virus (NANBV) infection. More specifically, it relates to diagnostic DNA fragments, diagnostic proteins, diagnostic antibodies and protective antigens and antibodies for an etiologic agent of NANB hepatitis, i.e., **hepatitis C virus.** Barr et al. (1986), Biotechniques 4:428.

Web site: http://appft1.uspto.gov/netahtml/PTO/search-bool.html

- **Hepatitis C virus assays**

  Inventor(s): Gao, Min; (Madison, CT), Lemm, Julie A.; (Durham, CT), Nower, Peter; (Wethersfield, CT), O'Boyle, Donald R.; (Clinton, CT), Rigat, Karen; (Clinton, CT), Sun, Jin-Hua; (North Haven, CT)

  Correspondence: Stephen B. Davis; Bristol-Myers Squibb Company; Patent Department; P O Box 4000; Princeton; NJ; 08543-4000; US

  Patent Application Number: 20040121975

  Date filed: August 12, 2003

  Abstract: The present invention includes an assay useful for identifying inhibitors of **Hepatitis C virus** (HCV) activity. Particularly, the present invention is directed to a dual HCV assay useful for high throughput screening that quantifies both the amount of HCV RNA replication inhibitory activity associated with a test compound and the amount of cytotoxicity associated with that test compound. The present invention also includes compounds discovered using this assay, compositions containing such compounds and methods of treating Hepatitis C by the administration of such compounds. The present invention also includes reporter assays using enzymes associated with HCV RNA replication, as well as a cell line having ATTC Accession No. PTA-4583.

  Excerpt(s): This application claims the benefit under 35 U.S.C. Section 119(e) of U.S. Provisional Patent Application No. 60/402,661 filed Aug. 12, 2002. The present invention includes assays useful for identifying inhibitors of **Hepatitis C virus** (HCV) activity. Particularly, the present invention includes a dual HCV assay useful for high throughput screening that quantifies both the amount of HCV RNA replication inhibitory activity associated with a test compound and the amount of cytotoxicity associated with the test compound. As such, an assay of the present invention permits the determination of both inhibitory activity associated with a test compound and selectivity of that test compound in a single well. The present invention also includes a reporter assay utilizing at least one enzyme associated with HCV RNA replication. The present invention also includes a cell line useful in assay of the present invention. Hepatitis C virus (HCV) is the major etiological agent of 90% of all cases of non-A, non-B hepatitis (Dymock, B. W. Emerging Drugs 6:13-42 (2001)). The incidence of HCV infection is becoming an increasingly severe public health concern with 2-15% individuals infected worldwide. While primary infection with HCV is often asymptomatic, most HCV infections progress to a chronic state that can persist for decades. Of those with chronic HCV infections, it is believed that about 20-50% will

eventually develop chronic liver disease (e.g. cirrhosis) and 20-30% of these cases will lead to liver failure or liver cancer. As the current HCV-infected population ages, the morbidity and mortality associated with HCV are expected to triple.

Web site: http://appft1.uspto.gov/netahtml/PTO/search-bool.html

- **Hepatitis C virus helicase crystals, crystallographic structure and methods**

  Inventor(s): Baldwin, Eric T.; (Portage, MI), Finzel, Barry C.; (Kalamazoo, MI), Harris, Melissa S.; (Marshall, MI)

  Correspondence: Mueting, Raasch & Gebhardt, P.A.; P.O. Box 581415; Minneapolis; MN; 55458; US

  Patent Application Number: 20040126809

  Date filed: May 2, 2001

  Abstract: Hepatitis C virus helicase has been crystallized as tetragonal and orthorhombic crystals, and the structures of the crystals has been solved. The structure coordinates of the crystal structures are useful for solving the structures of other molecules or molecular complexes.

  Excerpt(s): This application claims the benefit of U.S. Provisional Application Serial No. 60/201,598, filed May 3, 2000, which is incorporated herein by reference in its entirety. The invention relates to the crystallization and structure determination of **Hepatitis C virus** helicase. HCV NS3 helicase is an NTP-dependent enzyme that unwinds duplex RNA and RNA:DNA hybrid substrates during viral replication. Several laboratories have reported structures of this enzyme in different crystal forms (Yao et al., Nat. Struct. Biol., 4: 463-77 (1997); Cho et al., J. Biol. Chem., 273:15045-52 (1998)), including one complex with bound single-stranded DNA (Kim et al., Structure, 6:89-100 (1998)). HCV NS3 helicase was found to include three domains. Two of these domains (d1 and d2) include homologous oligonucleotide-binding motifs conserved across helicase superfamilies (Korolev et al., Protein Science, 7:605-10 (1998)) that are thought to bind to individual phosphates along the backbone of the oligonucleotide substrate (Kim et al., Structure, 6:89-100 (1998)).

  Web site: http://appft1.uspto.gov/netahtml/PTO/search-bool.html

- **Hepatitis C virus inhibitors**

  Inventor(s): Wang, Xiangdong Alan; (Guilford, CT), Campbell, Jeffrey Allen; (Cheshire, CT), Chen, Yan; (Guilford, CT), Good, Andrew Charles; (Wallingford, CT), Hewawasam, Piyasena; (Middletown, CT), Scola, Paul Michael; (Glastonbury, CT), Sin, Ny; (East Hampton, CT), Sit, Sing-Yuen; (Meriden, CT), Sun, Li-Qiang; (Glastonbury, CT)

  Correspondence: Stephen B. Davis; Bristol-Myers Squibb Company; Patent Department; P O Box 4000; Princeton; NJ; 08543-4000; US

  Patent Application Number: 20040106559

  Date filed: May 20, 2003

  Abstract: Hepatitis C virus inhibitors are disclosed having the general formula: 1wherein R.sub.1, R.sub.2, R.sub.3, R', B, Y and X are described in the

description.Compositions comprising the compounds and methods for using the compounds to inhibit HCV are also disclosed.

Excerpt(s): The non-provisional application claims priority from the provisional application U.S. S No. 60/382,055 filed May 20, 2002. The present invention is generally directed to antiviral compounds, and more specifically directed to compounds which inhibit the functioning of the NS3 protease encoded by **Hepatitis C virus** (HCV), compositions comprising such compounds and, methods for inhibiting the functioning of the NS3 protease. HCV is a major human pathogen, infecting an estimated 170 million persons worldwide--roughly five times the number infected by human immunodeficiency virus type 1. A substantial fraction of these HCV infected individuals develop serious progressive liver disease, including cirrhosis and hepatocellular carcinoma. (Lauer, G. M.; Walker, B. D. N. Engl. J. Med. (2001), 345, 41-52).

Web site: http://appft1.uspto.gov/netahtml/PTO/search-bool.html

- **Hepatitis C virus non-structural NS3/4A fusion gene**

Inventor(s): Sallberg, Matti; (Alvsjo, SE)

Correspondence: Knobbe Martens Olson & Bear Llp; 2040 Main Street; Fourteenth Floor; Irvine; CA; 92614; US

Patent Application Number: 20040092730

Date filed: August 15, 2001

Abstract: Disclosed herein is the discovery of a novel **hepatitis C virus** (HCV) isolated from a human patient. Embodiments of the inevntion include HCV peptides, nucleic acids encoding said HCV peptides, antibodies directed to said peptides, compositions containing said nucleic acids and peptides, as well as, methods of making and using the aforementioned compositions including, but not limited to, diagnostics and medicaments for the treatment and prevention of HCV infection.

Excerpt(s): This application claims priority to U.S. Provisional Patent Application Nos. 60/225,767 and 60/229,175, filed Aug. 17, 2000 and Aug. 29, 2000, respectively, and U.S. patent application Ser. No. 09/705,547, filed Nov. 3, 2000, all of which are hereby expressly incorporated by reference in their entireties. The present invention relates to the discovery of a novel **hepatitis C virus** (HCV) isolated from a human patient. Embodiments include novel HCV peptides, nucleic acids encoding said HCV peptides, antibodies directed to said peptides, compositions containing said nucleic acids and peptides, as well as methods of making and using the aforementioned compositions including, but not limited to, diagnostics and medicaments for the treatment and prevention of HCV infection. Viruses are intracellular parasites that require the biochemical machinery of a host cell for replication and propagation. All virus particles contain some genetic information that encodes viral structural proteins and enzymes. The genetic material may be DNA or RNA, in double- or single stranded form. (Virology, Fields ed., third edition, Lippencott-Raven publishers, pp 72-83 (1996)). The viral nucleic acid is surrounded by a coat of proteins called the capsid. (Id.) In some viruses the capsid is surrounded by an additional layer comprised of a lipid membrane, referred to as the envelope. (Id. at 83-95).

Web site: http://appft1.uspto.gov/netahtml/PTO/search-bool.html

- **Human monoclonal antibody against hepatitis c virus e2 glycoprotein**

  Inventor(s): Da Silva Cardoso, Marcia; (Oberelchingen, DE), Dagan, Shlomo; (Nes-Ziona, IL), Eren, Rachel; (Netaim, IL), Kubanek, Bernard; (Ulm, DE), Sifmoneit, Karl; (Dieburg, DE)

  Correspondence: Browdy And Neimark, P.L.L.C.; 624 Ninth Street, NW; Suite 300; Washington; DC; 20001-5303; US

  Patent Application Number: 20040071710

  Date filed: August 28, 2003

  Abstract: Disclosed is a hybridoma cell line which produces human antibodies capable of binding to the **hepatitis C virus** (HCV) E2 glycoprotein and capable of neutralizing HCV infection in vivo in an animal model, as well as antibodies produced by the cell line. Also disclosed are various uses of said antibodies in the prevention and treatment of HCV infection. Peripheral blood lymphocytes obtained from human donors having a high titer of anti HCV E2 antibodies are transformed in vitro by Epstein-Barr virus and then fused with heteromyeloma cells to generate hybridomas secreting human antibodies having a high affinity and specificity to HCV E2 glycoprotein.

  Excerpt(s): The present invention concerns a hybridoma cell line producing human antibodies capable of binding to **hepatitis C virus** envelope glycoprotein, antibodies produced by the cell line and various uses thereof. Hepatitis C virus (HCV) infection is a major worldwide health problem. Approximately 170 million individuals worldwide are infected by HCV and chronically infected patients carry a high risk of developing cirrhosis and hepatocellular carcinoma (Cohen 1999 Science 285:26-30). Interferon-.alpha. either alone or in combination with ribavirin is used for therapy of HCV showing efficacy in between 20% and 40% of patients respectively.

  Web site: http://appft1.uspto.gov/netahtml/PTO/search-bool.html

- **In vitro system for replication of RNA-dependent RNA polymerase (RDRP) viruses**

  Inventor(s): Jeffries, Matthew W.; (Wilmington, DE), King, Robert W.; (West Chester, PA), Pasquinelli, Claudio; (Media, PA)

  Correspondence: Stephen B. Davis; Bristol-Myers Squibb Company; Patent Department; P O Box 4000; Princeton; NJ; 08543-4000; US

  Patent Application Number: 20040126388

  Date filed: December 12, 2003

  Abstract: An in vitro method to conduct genomic replication of the viral genomes of viruses that utilize RNA-dependent RNA polymerase for replication (RDRP viruses), such as HCV. The method employs a construct comprising the 3' and 5' untranslated regions (UTRs) of the viral genome which are operably linked on the 5' and 3' ends of a reporter sequence, in antisense orientation, such that when viral replication is occurring within the cell which produces RDRP, the reporter protein will be made. The method of the invention provides an efficient means for measuring genomic replication in RDRP viruses, and also for the rapid screening of compounds for their ability to inhibit genomic replication of RDRP viruses, including the **Hepatitis C virus** (HCV).

  Excerpt(s): This application claims the benefit of U.S. Provisional Application No. 60/265,437, filed Jan. 31, 2001, the contents of which are herein incorporated by reference in their entirety. This invention is directed toward the pharmaceutical and

molecular biology arts, more particularly this invention is an in vitro system for the replication of the viral genomes of viruses that depend upon the enzyme RNA-dependent RNA polymerase (RDRP) for replication. The method of the invention provides an efficient means for measuring genomic replication in RDRP viruses, and also for the rapid screening of compounds for their ability to inhibit genomic replication of RDRP viruses, including the **Hepatitis C virus** (HCV). It is known that viral genomes can be made of DNA or RNA and can be double-stranded or single-stranded. Typically, viral genomes encode viral coat proteins that serve to package the genome after replication, and also nonstructural proteins that facilitate enzymatic replication of the viral genome in conjunction with cellular enzymes. In the case of some viruses having a single-stranded RNA genome, one of the nonstructural proteins encoded by the viral genome is RNA-dependent RNA polymerase (RDRP), which is needed by the virus to replicate its genomic sequence. The viral enzyme RNA-dependent RNA polymerase is also called RNA replicase.

Web site: http://appft1.uspto.gov/netahtml/PTO/search-bool.html

- **Inhibitors of serine proteases, particularly hepatitis C virus NS3 protease**

  Inventor(s): Bhisetti, Govinda Rao; (Lexington, MA), Farmer, Luc J.; (Foxboro, MA), Tung, Roger D.; (San Diego, CA)

  Correspondence: Vertex Pharmaceuticals INC.; 130 Waverly Street; Cambridge; MA; 02139-4242; US

  Patent Application Number: 20040077600

  Date filed: July 7, 2003

  Abstract: The present invention relates to compounds, methods and pharmaceutical compositions for inhibiting proteases, particularly serine proteases, and more particularly HCV NS3 proteases. The compounds, and the compositions and methods that utilize them, can be used, either alone or in combination to inhibit viruses, particularly HCV virus.

  Excerpt(s): The present invention relates to compounds that are useful as protease inhibitors, particularly as serine protease inhibitors, and more particularly as hepatitis C NS3 protease inhibitors. As such, they act by interfering with the life cycle of the **hepatitis C virus** and are also useful as antiviral agents. This invention also relates to pharmaceutical compositions comprising these compounds. The compounds and pharmaceutical compositions of this invention are particularly well suited for inhibiting HCV NS3 protease activity and consequently, may be advantageously used as therapeutic agents against the **hepatitis C virus** and other viruses that are dependent upon a serine protease for proliferation. This invention also relates to methods for inhibiting the activity of proteases, including **hepatitis C virus** NS3 protease and other serine proteases, using the compounds of this invention and related compounds. Infection by **hepatitis C virus** ("HCV") is a compelling human medical problem. HCV is recognized as the causative agent for most cases of non-A, non-B hepatitis, with an estimated human seroprevalence of 1% globally [Purcell, R. H., "Hepatitis C virus: Historical perspective and current concepts" FEMS Microbiology Reviews 14, pp. 181-192 (1994); Van der Poel, C. L., "Hepatitis C Virus. Epidemiology, Transmission and Prevention in **Hepatitis C Virus.** Current Studies in Hematology and Blood Transfusion, H. W. Reesink, Ed., (Basel: Karger), pp. 137-163 (1994)]. Four million individuals may be infected in the United States alone [Alter, M. J. and Mast, E. E., "The Epidemiology of

Viral Hepatitis in the United States, Gastroenterol. Clin. North Am. 23, pp. 437-455 (1994)].

Web site: http://appft1.uspto.gov/netahtml/PTO/search-bool.html

- **Method for detecting hepatitis C virus**

  Inventor(s): Lee, Tzong Hae; (San Francisco, CA)

  Correspondence: Stevens Davis Miller & Mosher, Llp; 1615 L Street, NW; Suite 850; Washington; DC; 20036; US

  Patent Application Number: 20040106099

  Date filed: December 2, 2002

  Abstract: A method for detecting **hepatitis C virus** (HCV) in a sample includes the steps of (a) extracting RENA from the sample; (b) contacting the RNA to a reverse transcriptase and a downstream primer specific to the HCV RINA sequence to create cDNA; (c) forming an amplification medium by mixing the cDNA with a PCR reaction mixture, a nucleic-acid-binding fluorescent entity, and the downstream primer and an upstream primer specific to the HCV RNA sequence; (d) thermally cycling the amplification medium between at least a denaturation temperature and an elongation temperature; (e) illuminating the amplification medium with a selected wavelength of light that is absorbed by the fluorescent entity during the thermally cycling step; (f) determining the amount of fluorescence generated by the fluorescent entity; and (g) detecting the presence of the target nucleic acid by analyzing the amount of luminescence determined after at least one amplification cycle.

  Excerpt(s): This invention relates to a method for detecting or quantifying **hepatitis C virus** (HCV) in a sample. Hepatitis C virus (HCV) is a major cause of acute hepatitis and chronic liver disease, including cirrhosis and liver cancer. It has been estimated by the World Health Organization (WHO) that 170 million persons are chronically infected with HCV and 3 to 4 million persons are newly infected each year. As is well known, **hepatitis C virus** is a small RNA virus containing a single, positive sense, molecule of RNA about 10,000 nucleotides in length. The cloning and sequencing of the HCV genome by Choo et al. (1989) has allowed the development of methods for detecting HCV infection via amplification of HCV RNA sequences by reverse transcription and cDNA polymerase chain reaction (RT-PCR) using primers derived from the HCV genomic sequence. However, traditional PCR methods do not allow accurate quantitation as the product is monitored beyond the exponential phase of PCR reaction and require laborious post-PCR processing. Moreover, methods such as enzyme immunosorbant assays (EIA) for the detection of HCV specific antibodies are not quantitative enough to reliably monitor decrease in viral reduction during antiviral therapy.

  Web site: http://appft1.uspto.gov/netahtml/PTO/search-bool.html

- **Method for replicating the hepatitis c virus**

  Inventor(s): Dubuisson, Jean; (Faches-Thumesnil, FR), Duverlie, Gilles; (Amiens, FR), Pillez, Andre; (Lille, FR), Wychowski, Czeslaw; (Meurchin, FR)

  Correspondence: Young & Thompson; 745 South 23rd Street 2nd Floor; Arlington; VA; 22202

  Patent Application Number: 20040142320

  Date filed: March 9, 2004

  Abstract: The invention concerns the use of cells capable or carrying out a process of prenylation of proteins coded by the **hepatitis C virus** (HCV) genome, such as prenylation of the NS5A protein, for replicating and, if required, the production of HCV or derivative viable mutants, in a suitable culture medium.

  Excerpt(s): The invention relates to a process for replicating the **hepatitis C virus.** The invention also relates to a process for screening inhibitors of the **hepatitis C virus.** The **hepatitis C virus** or HCV, identified in 1989 by Choo's team (Choo et al., 1989), is the major agent of the viral infections that have for long been called non-A non-B hepatitides. The term "non-A non-B" was introduced in the 70s to describe hepatitides of which the etiological agents, not yet identified, appear serologically different from hepatitides A and B, thanks to the introduction of immunological tests (Feinstone et al., 1975; Prince et al., 1974). In clinical terms, infection by the **hepatitis C virus** is characterized by a strong predominance of the asymptomatic forms and the frequency of the evolution towards chronicity.

  Web site: http://appft1.uspto.gov/netahtml/PTO/search-bool.html

- **Method for simultaneously detecting an antigen of, and and antibody against, an infectious microorganism**

  Inventor(s): Feyssaguet, Muriel; (Saint Cloud, FR), Henriot, Stephanie; (Suresnes, FR), Lambert, Nadine; (Chatou, FR), Rieunier, Francois; (Bois D'Arcy, FR)

  Correspondence: Jacobson Holman Pllc; 400 Seventh Street N.W.; Suite 600; Washington; DC; 20004; US

  Patent Application Number: 20040072267

  Date filed: May 8, 2003

  Abstract: The invention relates to a method for detecting, in vitro, an infection with a microorganism, such as the **hepatitis C virus,** in a biological sample, by simultaneously detecting an antigen of this microorganism and the antibodies against this same antigen, and also to the reagents and kits implementing this method.

  Excerpt(s): The invention relates to the in vitro detection of an infection with an infectious, in particular viral, microorganism, and in particular the in vitro detection of an infection with a **hepatitis C virus** (HCV). More precisely, the invention also relates to a method for simultaneously detecting an antigen of an infectious, in particular viral, microorganism, and antibodies directed against this same infectious microorganism, and also to the reagents and kits implementing it. More particularly, it relates to a method for simultaneously detecting HCV antigen and anti-HCV antibodies, and to the reagents and kits implementing it. Infection with the **hepatitis C virus,** a form of hepatitis initially referred to as hepatitis non-A, non-B, is a preoccupying health problem which has been recognized for a long time, in particular in blood transfusion.

Patent application EP 318 216 published on May 31, 1989, describes the cloning of fragments of cDNA of a virus responsible for hepatitis C in humans, called HCV. It also describes the sequence of five genes encoding the nonstructural proteins (NS1 to NS5) of the virus (approximately 78% of the total genome of HCV), the C100-3 antigen (which contains 363 amino acids of the NS3-NS4 region and is fused to superoxide dismutase) and also a method for detecting anti-HCV antibodies using the C100-3 antigen. This "first generation" method for detecting anti-HCV antibodies made it possible, inter alia, to establish that HCV is a major cause of hepatitis non-A, non-B, now called hepatitis C in the world. However, this method does not make it possible to detect more than 70 to 80% of the sera infected with the virus. This lack of sensitivity does not allow early detection of the infections either.

Web site: http://appft1.uspto.gov/netahtml/PTO/search-bool.html

- **Method for the use of pyranoindole derivatives to treat infection with Hepatitis C virus**

  Inventor(s): Burns, Christopher J.; (Malvern, PA), Collett, Marc S.; (Collegeville, PA), Condon, Stephen M.; (Glenmoore, PA), Ellingboe, John W.; (Ridgewood, NJ), Gopalsamy, Ariamala; (Mahwah, NJ), Laporte, Matthew G.; (Honey Brook, PA), Mansour, Tarek S.; (New City, NY), Park, Kaapjoo; (Suffern, NY)

  Correspondence: Fitzpatrick Cella Harper & Scinto; 30 Rockefeller Plaza; New York; NY; 10112; US

  Patent Application Number: 20040082643

  Date filed: May 20, 2003

  Abstract: The invention is directed to methods of treating, preventing, or inhibiting a Hepatitis C viral infection in a mammal comprising contacting the mammal with an effective amount of a compound of the formula: 1Wherein substitutions at R.sub.1, R.sub.2 , R.sub.3-R.sub.12, and Y are set forth in the specification.

  Excerpt(s): This application claims the benefit of U.S. Provisional Application No. 60/382,154, filed on May 21, 2002, and U.S. Provisional Application No. 60/458,706, filed Mar. 28, 2003. These applications are hereby incorporated by reference. This invention is directed to pyranoindole derivatives, pharmaceutical compositions containing them, and to their use in the treatment of Hepatitis C viral infections, either alone or in conjunction with one or more biologically active agents, either concurrently or sequentially. Hepatitis C is a common viral infection that can lead to chronic Hepatitis, cirrhosis, liver failure, and hepatocellular carcinoma. Infection with the **Hepatitis C virus** (HCV) leads to chronic Hepatitis in at least 85% of cases, is the leading reason for liver transplantation, and is responsible for at least 10,000 deaths annually in the United States (Hepatology, 1997, 26 (Suppl. 1), 2S-10S).

  Web site: http://appft1.uspto.gov/netahtml/PTO/search-bool.html

- **Method of detection of HCV antibodies in combination assay or sole antibody assay**

  Inventor(s): Cheng, Yu; (Mundelein, IL), Shah, Dinesh O.; (Libertyville, IL), Stewart, James L.; (Libertyville, IL)

  Correspondence: Steven F. Weinstock; Abbott Laboratories; 100 Abbott Park Road; DEPT. 377/ap6a; Abbott Park; IL; 60064-6008; US

  Patent Application Number: 20040152070

  Date filed: February 4, 2003

  Abstract: The subject invention relates to methods for the simultaneous detection of **Hepatitis C Virus** (HCV) antigens as well as antibodies produced in response to HCV antigens. Such methods may be carried out in the presence of a diluent comprising a reductant or lacking a reductant. Furthermore, the performance of such methods may be maximized by altering such variables as the nature of the antigen coated on the solid phase, temperature application and time.

  Excerpt(s): The subject invention relates to an improved method for the detection of **Hepatitis C Virus** (HCV) antibodies, whether said antibodies are being detected in a combination assay (which detects both HCV antigens and antibodies) or in an assay which detects only HCV antibodies. Recent epidemiological studies indicate that HCV infects more than 170 million people worldwide and that, in more than 50% of the cases, the infection is chronic. In the United States, there are approximately 4 million people infected, and 30,000 new infections are estimated to occur annually (NIH Conference, Hepatology Suppl 1:2S (1997)). In addition, HCV is responsible for 8,000-10,000 deaths annually in the United States and is the leading indicator for liver transplantation. The HCV genome is a single-stranded RNA molecule of positive polarity that is approximately 9400-9500 nucleotides in length. The organization of the coding regions resembles that of other flaviviruses [Major et al., Hepatology 25:1527 (1997)] as well as the more recently discovered GB viruses [Muerhoff AS, et al., J Virol 69:5621 (1995)]. The HCV genome possesses a large open reading frame (ORF) encoding a polyprotein precursor of 3010 to 3033 amino acids depending on the particular isolate [Choo et al., Proc Natl Acad Sci USA 88:2451 (1991); Grakoui et al., J Virol 67:1385 (1993)]. HCV structural genes (core and envelope) are encoded near the 5'-end of the genome, followed by the proteases and helicase, the helicase cofactor and the replicase. Noncoding regions (NCR), thought to be important in replication, are found at each end of the genome.

  Web site: http://appft1.uspto.gov/netahtml/PTO/search-bool.html

- **Methods and compositions for treating hepatitis C Virus**

  Inventor(s): LaColla, Paulo; (Cagliari, IT), Sommadossi, Jean-Pierre; (Birmingham, AL)

  Correspondence: King & Spalding; 191 Peachtree Street, N.E.; Atlanta; GA; 30303-1763; US

  Patent Application Number: 20040097461

  Date filed: June 20, 2003

  Abstract: A method and composition for treating a host infected with hepatitis C comprising administering an effective hepatitis C treatment amount of a described 1', 2' or 3'-modified nucleoside or a pharmaceutically acceptable salt or prodrug thereof, is provided.

Excerpt(s): This invention is in the area of pharmaceutical chemistry, and is in particular, is a compound, method and composition for the treatment of **hepatitis C virus.** This application claims priority to U.S. provisional application No. 60/206,585, filed on May 23, 2000. The **hepatitis C virus** (HCV) is the leading cause of chronic liver disease worldwide. (Boyer, N. et al. J. Hepatol. 32:98-112, 2000). HCV causes a slow growing viral infection and is the major cause of cirrhosis and hepatocellular carcinoma (Di Besceglie, A. M. and Bacon, B. R., Scientific American, Oct.: 80-85, (1999); Boyer, N. et al. J. Hepatol. 32:98-112, 2000). An estimated 170 million persons are infected with HCV worldwide. (Boyer, N. et al. J Hepatol. 32:98-112, 2000). Cirrhosis caused by chronic hepatitis C infection accounts for 8,000-12,000 deaths per year in the United States, and HCV infection is the leading indication for liver transplant. HCV is known to cause at least 80% of posttransfusion hepatitis and a substantial proportion of sporadic acute hepatitis. Preliminary evidence also implicates HCV in many cases of "idiopathic" chronic hepatitis, "cryptogenic" cirrhosis, and probably hepatocellular carcinoma unrelated to other hepatitis viruses, such as Hepatitis B Virus (HBV). A small proportion of healthy persons appear to be chronic HCV carriers, varying with geography and other epidemiological factors. The numbers may substantially exceed those for HBV, though information is still preliminary; how many of these persons have subclinical chronic liver disease is unclear. (The Merck Manual, ch. 69, p. 901, 16th ed., (1992)).

Web site: http://appft1.uspto.gov/netahtml/PTO/search-bool.html

- **Methods for identifying inhibitors of helicase activity from hepatitis C virus**

  Inventor(s): Collett, Marc S.; (Collegeville, PA), Groarke, James M.; (Phoenixville, PA), Pevear, Daniel C.; (Harleysville, PA), Young, Dorothy C.; (Collegeville, PA)

  Correspondence: Dann, Dorfman, Herrell & Skillman; 1601 Market Street; Suite 2400; Philadelphia; PA; 19103-2307; US

  Patent Application Number: 20040076949

  Date filed: October 10, 2003

  Abstract: Assay methods are disclosed having utility in the identification of therapeutic agents effective against human **hepatitis C virus** and related viruses. NS3 protein derived from these viruses, representing a native and authentic version of the complete protein sequence, is used in the assay methods of the invention, which enables identification and development of anti-viral agents exhibiting inhibition of the protein's NTPase and RNA helicase activities.

  Excerpt(s): This application is a continuation of U.S. patent application Ser. No. 08/678,771 filed Jul. 11, 1996, which in turn claims priority from U.S. Provisional Application 60/010,474 filed Jan. 23, 1996, the entire disclosure of each being incorporated by reference herein. The present invention relates to the fields of molecular biology and biochemistry. More specifically, the invention provides materials and methodology for the identification and development of agents capable of inhibiting the essential nucleoside triphosphatase (NTPase) and RNA helicase activities of certain RNA viruses, particularly human hepatitis C and related viruses. Several publications are referenced in this application by numerals in parenthesis in order to more fully describe the state of the art to which this invention pertains, as well as to aid in describing the invention itself. Full citations for these references are found at the end of the specification. Each of these publications is incorporated herein by reference.

  Web site: http://appft1.uspto.gov/netahtml/PTO/search-bool.html

- **Methods for treating viral infection using IL-28 and IL-29**

  Inventor(s): Henderson, Katherine E.; (Seattle, WA), Kindsvogel, Wayne R.; (Seattle, WA), Klucher, Kevin M.; (Bellevue, WA), Sivakumar, Pallavur V.; (Seattle, WA)

  Correspondence: Deborah A. Sawislak; Zymogenetics, INC.; 1201 Eastlake Avenue East; Seattle; WA; 98102; US

  Patent Application Number: 20040138122

  Date filed: October 23, 2003

  Abstract: IL-28A, IL-28B, IL-29, and certain mutants thereof have been shown to have antiviral activity on a spectrum of viral species. Of particular interest is the antiviral activity demonstrated on viruses that infect liver, such as hepatitis B virus and **hepatitis C virus.** In addition, IL-28A, IL-28B, IL-29, and mutants thereof do not exhibit some of the antiproliferative activity on hematopoietic cells that is observed with interferon treatment. Without the immunosuppressive effects accompanying interferon treatment, IL-28A, IL-28B, and IL-29 will be useful in treating immunocompromised patients for viral infections.

  Excerpt(s): This application claims the benefit of U.S. Provisional Application Serial No. 60/420,714, filed Oct. 23, 2002, U.S. Provisional Application Serial No. 60/463,939, filed Apr. 18, 2003, U.S. Provisional Application Serial No. 60/420,713, filed Oct. 23, 2002, and U.S. Provisional Application Serial No. 60/463,982, filed Apr. 18, 2003, all of which are herein incorporated by reference. Strategies for treating infectious disease often focus on ways to enhance immunity. For instance, the most common method for treating viral infection involves prophylactic vaccines that induce immune-based memory responses. Another method for treating viral infection includes passive immunization via immunoglobulin therapy (Meissner, J. Pediatr. 124:S17-21, 1994). Administration of Interferon alpha (IFN-.alpha.) is another method for treating viral infections such as genital warts (Reichman et al., Ann. Intern. Med. 108:675-9, 1988) and chronic viral infections like **hepatitis C virus** (HCV) (Davis et al., New Engl. J. Med. 339:1493-9, 1998) and hepatitis B virus (HBV). For instance, IFN-.alpha. and IFN-.beta. are critical for inhibiting virus replication (reviewed by Vilcek et al., (Eds.), Interferons and other cytokines. In Fields Fundamental Virology., 3.sup.rd ed., Lippincott-Raven Publishers Philadelphia, Pa., 1996, pages 341-365). In response to viral infection, CD4+ T cells become activated and initiate a T-helper type I (TH1) response and the subsequent cascade required for cell-mediated immunity. That is, following their expansion by specific growth factors like the cytokine IL-2, T-helper cells stimulate antigen-specific CD8+ T-cells, macrophages, and NK cells to kill virally infected host cells. Although oftentimes efficacious, these methods have limitations in clinical use. For instance, many viral infections are not amenable to vaccine development, nor are they treatable with antibodies alone. In addition, IFN's are not extremely effective and they can cause significant toxicities; thus, there is a need for improved therapies. Not all viruses and viral diseases are treated identically because factors, such as whether an infection is acute or chronic and the patient's underlying health, influence the type of treatment that is recommended. Generally, treatment of acute infections in immunocompetent patients should reduce the disease's severity, decrease complications, and decrease the rate of transmission. Safety, cost, and convenience are essential considerations in recommending an acute antiviral agent. Treatments for chronic infections should prevent viral damage to organs such as liver, lungs, heart, central nervous system, and gastrointestinal sytem, making efficacy the primary consideration.

Web site: http://appft1.uspto.gov/netahtml/PTO/search-bool.html

- **Methods of infection with hepatitis c virus**

  Inventor(s): Katsume, Asao; (Shizuoka, JP), Kohara, Michinori; (Tokyo, JP)

  Correspondence: Davidson, Davidson & Kappel, Llc; 485 Seventh Avenue, 14th Floor; New York; NY; 10018; US

  Patent Application Number: 20040101827

  Date filed: April 2, 2003

  Abstract: The present invention relates to a method for efficiently infecting a small animal with **hepatitis C virus.** Specifically, the present invention relates to a method for infecting a small animal with **hepatitis C virus,** which comprises a step of administering RNA containing the genomic RNA of **hepatitis C virus** into the liver, or a step of administering to a small animal the culture supernatant of an animal cell having a vector that contains cDNA corresponding to the genomic RNA of **hepatitis C virus** introduced therein, and relates to a small animal infected with **hepatitis C virus** by these methods. The present invention further relates to a method for screening for remedies against hepatitis C virus-associated diseases, or substances that inhibit the growth of **hepatitis C virus** using the yield of the virus as an indicator.

  Excerpt(s): The present invention relates to methods for efficiently infecting small animals with **hepatitis C virus** (hereinafter, referred to as "HCV"). The infection methods of the present invention can improve HCV infection rate, so that they are useful in the production of hepatitis C model animals. The present invention further relates to novel screening methods that are useful in searching for remedies against HCV-associated diseases or substances that inhibit the growth of HCV. HCV is a major causative virus of post-transfusion non-A, non-B hepatitis (Saito, I. et al., Proc. Natl. Acad. Sci. USA, 87, 6547-6549 (1990)). Hepatitis caused by this virus develops at a high rate into chronic hepatitis, and cirrhosis and hepatoma, so that hepatitis is a disease for which the discovery of reliable therapeutic measures is an urgent concern. The cDNA of this virus was cloned by Choo et al in 1989 (Choo, Q. -L., et al., Science, 244, 359-362 (1989)), and the virus is known to be a single stranded RNA virus belonging to the Flavivirus family (Kato, N., et al., Proc. Natl. Acad. Sci., USA, 87, 9524-9528 (1990)). To date, the entire nucleotide sequence and the amino acid sequence have been elucidated by several research groups (Kato, N., et al., Proc. Natl. Acad. Sci., USA, 87, 9524-9528 (1990), Proc. Natl. Acad. Sci., USA, 88, 2451-2455 (1991), J. Virol., 65, 1105-1113 (1991), J. Gen. Virol., 72, 2697-2704 (1991), Virology, 188, 331-341 (1992)). There have been many reports concerning HCV as described above, however, HCV is still poorly understood. For example, the mechanisms of HCV including infection, replication, extracellular release and the like are almost unknown under the present state of knowledge. Elucidation of these mechanisms are delayed because, for example, the number of types of animals that can be infected with HCV is limited, the production of appropriate disease model animals is difficult, and a simple screening system for studying anti-HCV action has not yet been established.

  Web site: http://appft1.uspto.gov/netahtml/PTO/search-bool.html

- **Multi-mer peptides derived from hepatitis C virus envelope proteins for diagnostic use and vaccination purposes**

  Inventor(s): Depla, Erik; (Dealalbergen, BE), Maertens, Geert; (Brugge, BE)

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  Patent Application Number: 20040126754

  Date filed: October 16, 2003

  Abstract: Multimer peptides (e.g. 30- to 45-mer peptides) derived from **hepatitis C virus** envelope proteins reacting with the majority of anti-HCV antibodies present in patient sera are described. The usage of the latter peptides to diagnose, and to vaccinate against, an infection with **hepatitis C virus** is also disclosed.

  Excerpt(s): The present invention relates to multi-mer peptides derived from **hepatitis C virus** envelope proteins which react with the majority of anti-HCV antibodies present in patient sera. Consequently, the present invention relates to the usage of the latter peptides to diagnose, and to vaccinate against, an infection with **hepatitis C virus.** Hepatitis C virus (HCV) infection is a major health problem in both developed and developing countries. It is estimated that about 1 to 5% of the world population is affected by the virus, amounting up to 175 million chronic infections worldwide. HCV infection appears to be the most important cause of transfusion-associated hepatitis and frequently progresses to chronic liver damage. Moreover, there is evidence implicating HCV in induction of hepatocellular carcinoma. Consequently, the demand for reliable diagnostic methods and effective therapeutic agents is high. There is also an urgent need to characterize new epitopes which can be used in the design of effective vaccines against hepatitis C. HCV is a positive stranded RNA virus of about 9,8 kilobases which code for at least three structural and at least six non-structural proteins. The structural proteins have not yet been functionally assigned, but are thought to consist of a single core protein and two envelope proteins E1 and E2. The E1 protein consists of 192 amino acids and contains 5 to 6 N-glycosylation sites, depending on the HCV genotype, whereas the E2 protein consists of 363 to 370 amino acids and contains up to 11 N-glycosylation sites, depending on the HCV genotype (for review see Maertens and Stuyver, 1997).

  Web site: http://appft1.uspto.gov/netahtml/PTO/search-bool.html

- **Novel hepatitis C virus peptides and uses thereof**

  Inventor(s): Branch, Andrea D.; (New York, NY), Stump, Decherd D.; (New York, NY), Walewski, Jose L.; (Eastchester, NY)

  Correspondence: Lahive & Cockfield, LLP.; 28 State Street; Boston; MA; 02109; US

  Patent Application Number: 20040156862

  Date filed: June 20, 2003

  Abstract: Novel **hepatitis C virus** (HCV) polypeptides are provided which are not encoded by the standard HCV open reading frame. These alternate reading frame polypeptides are useful, inter alia, in vaccine compositions, in diagnosing HCV infection, and as therapeutic targets.

  Excerpt(s): The present application is a Continuation of U.S. patent application Ser. No. 09/719,277, filed Apr. 13, 2001, which is a National Stage of PCT/US99/12929, filed Jun.

9, 1999, which claims benefit of Provisional Application 60/089,138, filed Jun. 11, 1998 and 60/088,670 filed Jun. 9, 1998, entitled "Novel **Hepatitis C Virus** Peptides and Uses Thereof", the entire contents of which are expressly incorporated by reference. Hepatitis C virus (HCV) is closely related to both the pestivirus and flavivirus genera in the Flaviviridae family. HCV is a single stranded RNA virus; the viral genome is approximately 9.5 kb. HCV RNA is positive sense and has a unique open reading frame which encodes a single polyprotein (Clarke. 1997. J. Gen. Virol. 78:2397). The polyprotein is proteolyticly processed to yield the mature viral proteins which include: nucleocapsid, envelope 1, envelope 2, metalloprotease, serine protease, RNA helicase, cofactor, and RNA polymerase. HCV is a major human pathogen. The virus was found to be the cause of most cases of hepatitis which could not be ascribed to hepatitis A, hepatitis B, or hepatitis delta virus (Clarke, supra). Over fifty percent of patients with **hepatitis C virus** (HCV) become chronic carriers of the virus; there may be as many as 500 million chronic carriers worldwide (Dhillon and Ducheiko. 1995. Histopathology 26: 297). Persistent infection with the virus causes chronic hepatitis and may ultimately lead to cirrhosis and/or cancer (Kuo et al. 1989. Science 244:362). Current therapies for HCV are ineffective, consequently there is a need for new approaches to treat HCV infection.

Web site: http://appft1.uspto.gov/netahtml/PTO/search-bool.html

- **Nucleoside derivatives for treating hepatitis C virus infection**

  Inventor(s): Dyatkina, Natalia B.; (Mountain View, CA), Hanson, Eric Jason; (San Francisco, CA), Keicher, Jesse D.; (Menlo Park, CA), Liehr, Sebastian Johannes Reinhard; (East Palo Alto, CA), Roberts, Christopher Don; (Belmont, CA)

  Correspondence: Burns, Doane, Swecker & Mathis, L.L.P.; P.O. Box 1404; Alexandria; VA; 22313-1404; US

  Patent Application Number: 20040063658

  Date filed: May 6, 2003

  Abstract: Disclosed are compounds, compositions and methods for treating **hepatitis C virus** infections.

  Excerpt(s): This application claims the benefit of U.S. Provisional Application Serial No. 60/378,624, filed on May 6, 2002 and U.S. Provisional Application Serial No. 60/392,871, filed on Jun. 28, 2002, the disclosures of which are incorporated herein in their entirety. The invention relates to the field of pharmaceutical chemistry, in particular to compounds, compositions and methods for treating **hepatitis C virus** infections. 6. Ducrocq, C.; et al., Tetrahedron, 32:773 (1976).

  Web site: http://appft1.uspto.gov/netahtml/PTO/search-bool.html

- **Peptide inhibitors of hepatitis C virus NS3 protease**

  Inventor(s): Priestley, E. Scott; (Hockessin, DE)

  Correspondence: Stephen B. Davis; Bristol-Myers Squibb Company; Patent Department; P O Box 4000; Princeton; NJ; 08543-4000; US

  Patent Application Number: 20040147483

  Date filed: January 15, 2004

Abstract: This invention relates to a novel class of peptides having the Formula (I): 1which are useful as serine protease inhibitors, and more particularly as **Hepatitis C virus** (HCV) NS3 protease inhibitors. This invention also relates to pharmaceutical compositions comprising these compounds and methods of using the same in the treatment of HCV infection.

Excerpt(s): The present invention relates generally to a novel class of peptides, which are useful as serine protease inhibitors, and more particularly as **Hepatitis C virus** (HCV) NS3 protease inhibitors. This invention also relates to pharmaceutical compositions comprising these compounds and methods of using the same in the treatment of HCV infection. Hepatitis C virus is the major cause of transfusion and community--acquired non-A, non-B hepatitis worldwide. Approximately 2% of the world's population are infected with the virus. In the Unites States, hepatitis C represents approximately 20% of cases of acute hepatitis. Unfortunately, self-limited hepatitis is not the most common course of acute HCV infection. In the majority of patients, symptoms of acute hepatitis resolve, but alanine aminotransferase (a liver enzyme diagnostic for liver damage) levels often remain elevated and HCV RNA persists. Indeed, a propensity to chronicity is the most distinguishing characteristic of hepatitis C, occurring in at least 85% of patients with acute HCV infection. The factors that lead to chronicity in hepatitis C are not well defined. Chronic HCV infection is associated with increased incidence of liver cirrhosis and liver cancer. No vaccines are available for this virus, and current treatment is restricted to the use of alpha interferon, which is effective in only 15-20% of patients. Recent clinical studies have shown that combination therapy of alpha interferon and ribavirin leads to sustained efficacy in 40% of patients (Poynard, T. et al. Lancet (1998), 352, 1426-1432.). However, a majority of patients still either fail to respond or relapse after completion of therapy. Thus, there is a clear need to develop more effective therapeutics for treatment of HCV-associated hepatitis. HCV is a positive-stranded RNA virus. Based on comparison of deduced amino acid sequence and the extensive similarity in the 5' untranslated region, HCV has been classified as a separate genus in the Flaviviridae family, which also includes flaviviruses such as yellow fever virus and animal pestiviruses like bovine viral diarrhea virus and swine fever virus. All members of the Flaviviridae family have enveloped virions that contain a positive stranded RNA genome encoding all known virus-specific proteins via translation of a single, uninterrupted, open reading frame.

Web site: http://appft1.uspto.gov/netahtml/PTO/search-bool.html

- **Peptides and their use as inhibitors of hepatitis c virus ns3 protease**

Inventor(s): Colarusso, Stefania; (Pomezia, IT), Gardelli, Cristina; (Pomezia, IT), Gerlach, Benjamin; (Arco, IT), Harper, Steven; (Pomezia, IT), Koch, Uwe; (Pomezia, IT), Matassa, Victor Giulio; (Hirschberg, DE), Muraglia, Ester; (Pomezia, IT), Narjes, Frank; (Pomezia, IT), Ontoria Ontoria, Jesus Maria; (Pomezia, IT), Petrocchi, Alessia; (Pomezia, IT), Ponzi, Simona; (Pomezia, IT), Stansfield, Ian; (Pomezia, IT)

Correspondence: Merck & Company Inc; 126 East Lincoln Avenue; Rahway; NJ; 07065; US

Patent Application Number: 20040142876

Date filed: March 3, 2004

Abstract: Compounds of formula (I), and pharmaceutically acceptable salts and esters thereof: (I); wherein Q, R2, X, Y and Z are as defined herein; are inhibitors of the **hepatitis C virus** (HCV) NS3 protease. 1

Excerpt(s): This invention relates to compounds which can act as inhibitors of the **hepatitis C virus** (HCV) NS3 protease, to uses of such compounds and to their preparation. The **hepatitis C virus** (HCV) is the major causative agent of parenterally-transmitted and sporadic non-A, non-B hepatitis (NANB-H). Some 1% of the human population of the planet is believed to be affected. Infection by the virus can result in chronic hepatitis and cirrhosis of the liver, and may lead to hepatocellular carcinoma. Currently no vaccine nor established, therapy exists, although partial success has been achieved in a minority of cases by treatment with recombinant interferon-.alpha., either alone or in combination with ribavirin. There is therefore a pressing need for new and broadly-effective therapeutics. Several virally-encoded enzymes are putative targets for therapeutic intervention, including a metalloprotease (NS2-3), a serine protease (NS3), a helicase (NS3), and an RNA-dependent RNA polymerase (NS5B). The NS3 protease is located in the N-terminal domain of the NS3 protein, and is considered a prime drug target since it is responsible for an intramolecular cleavage at the NS3/4A site and for downstream intermolecular processing at the NS4A/4B, NS4B/5A and NS5A/5B junctions.

Web site: http://appft1.uspto.gov/netahtml/PTO/search-bool.html

- **Structural targets in hepatittis c virus ires element**

  Inventor(s): Puglisi, Joseph D.; (Stanford, CA)

  Correspondence: Bozicevic, Field & Francis Llp; 200 Middlefield RD; Suite 200; Menlo Park; CA; 94025; US

  Patent Application Number: 20040073380

  Date filed: September 8, 2003

  Abstract: Molecular structures, computer representations thereof, and methods of analysis are provided for the **hepatitis C virus** internal ribosome entry site (HCV IRS). Novel features of the structure include the tetaloop fold in domain IIIe, including the array of three major groove exposed Watson-Crick faces (G295, A296, and U297), which loop has been found to be a point of direct contact with the 40S subunit; and the structure comprising the domain IIId loop E and hairpin loop backdone reversion, which places two S turns on the same side of hairpin loop structure.

  Excerpt(s): Hepatitis C virus (HCV) is spread primarily through contact with infected blood and can cause cirrhosis, irreversible and potentially fatal liver scarring, liver cancer, or liver failure. It can lie dormant for 10 years or more before symptoms appear. Some patients will have no symptoms of liver damage, and their liver enzymes will stay at normal levels. Other patients have severe hepatitis C, with detectable HCV in their blood, liver enzymes elevated as much as 20 times more than normal, and a prognosis of ultimately developing cirrhosis and end-stage liver disease. The disease is responsible for between 8,000 and 10,000 deaths yearly, and is the major reason for liver transplants in the United States, accounting for 1,000 of the procedures annually. Chronic hepatitis C varies widely in its severity and outcome. Presently, there is no vaccine or other means of preventing hepatitis C infection. HCV exists in many genotypes, making it difficult for researchers in their quest to develop a vaccine effective for all variations. Also, HCV mutates frequently within infected patients, so even if an effective vaccine is developed, it could be rendered useless by a new strain of mutant virus. Currently, chronic hepatitis C patients who do not respond to therapy have few options. The only approved treatment for infection is interferon, which may be combined with other active agents.

Web site: http://appft1.uspto.gov/netahtml/PTO/search-bool.html

- **Substituted aryl thioureas and related compounds; inhibitors of viral replication**

  Inventor(s): Chen, Dawei; (Middletown, CT), Deshpande, Milind; (Madison, CT), Li, Shouming; (Cheshire, CT), Liu, Cuixian; (Branford, CT), Ohkanda, Junko; (Tokyo, JP), Phadke, Avinash; (Branford, CT), Quinn, Jesse; (Windsor, CT), Shen, Yiping; (Branford, CT), Thurkauf, Andrew; (Ridgefield, CT), Wang, Xiangzhu; (Branford, CT)

  Correspondence: Cantor Colburn, Llp; 55 Griffin Road South; Bloomfield; CT; 06002

  Patent Application Number: 20040138205

  Date filed: November 18, 2003

  Abstract: The invention provides compounds and pharmaceutically acceptable salts of Formula I 1wherein the variables A.sub.1, A.sub.2, R.sub.1, R.sub.2, V, W, X, Y, and Z are defined herein. Certain compounds of Formula I described herein which possess potent antiviral activity. The invention particularly provides compounds of Formula I that are potent and/or selective inhibitors of **Hepatitis C virus** replication. The invention also provides pharmaceutical compositions containing one or more compound of Formula I, or a salt, solvate, or acylated prodrug of such compounds, and one or more pharmaceutically acceptable carriers, excipients, or diluents.The invention further comprises methods of treating patients suffering from certain infectious diseases by administering to such patients an amount of a compound of Formula I effective to reduce signs or symptoms of the disease or disorder. These infectious diseases include viral infections, particularly HCV infections. The invention is particularly includes methods of treating human patients suffering from an infectious disease, but also encompasses methods of treating other animals, including livestock and domesticated companion animals, suffering from an infectious disease.Methods of treatment include administering a compound of Formula I as a single active agent or administering a compound of Formula I in combination with on or more other therapeutic agent.

  Excerpt(s): This application claims priority from U.S. Provisional Application No. 60/427,634 filed Nov. 19, 2002. The present invention provides arylthiourea derivatives and related compounds, useful as antiviral agents. Certain arylthiourea derivatives and related compounds disclosed herein are potent and/or selective inhibitors of viral replication, particularly **Hepatitis C virus** replication. The invention also provides pharmaceutical compositions containing one or more arylthiourea derivative or related compound and one or more pharmaceutically acceptable carriers, excipients, or diluents. Such pharmaceutical compositions may contain an arylthiourea derivative or related compound as the only active agent or may contain a combination of an arylthiourea derivative or related compound and one or more other pharmaceutically active agents. The invention also provides methods for treating Hepatitis C viral infections in mammals. In the 1940's the disease originally referred to as viral hepatitis was distinguished into two separate disorders termed infectious hepatitis (hepatitis A, HAV) and homologous serum hepatitis (hepatitis B, HBV). Transfusion of blood products had been demonstrated to be a common route of transmission of viral hepatitis. HBV was originally assumed to be the causative agent of post-transfusion hepatitis as the epidemiological and clinical features of the disorder did not fit those of HAV.

  Web site: http://appft1.uspto.gov/netahtml/PTO/search-bool.html

- **Therapeutic targets for treatment of HCV infections, methods of treating HCV infections and compounds useful therefor**

  Inventor(s): Cotten, Matthew; (Munchen, DE), Herget, Thomas; (Planegg, DE), Klebl, Bert; (Munchen, DE), Obert, Sabine; (Munchen, DE)

  Correspondence: Leon R. Yankwich; Yankwich & Associates; 201 Broadway; Cambridge; MA; 02139; US

  Patent Application Number: 20040152073

  Date filed: November 26, 2003

  Abstract: The present invention relates to the human cellular protein glutathione peroxidase-gastrointestinal as a target for medical intervention against **Hepatitis C virus** (HCV) infections. Furthermore, the present invention relates to a method for the detection of compounds useful for prophylaxis and/or treatment of **Hepatitis C virus** infections and a method for detecting **Hepatitis C virus** infections in an individual or in cells. Also compositions, compounds, nucleic acid molecules (such as aptamers), mono- or polyclonal antibodies are disclosed which are effective for the treatment of HCV infections, and methods for prophylaxis and/or treatment of **Hepatitis C virus** infections or for the regulation of **Hepatitis C virus** production are disclosed.

  Excerpt(s): The present application is a continuation-in-part of copending U.S. application Ser. No. 10/342,054, filed Jan. 14, 2003, which is a continuation-in-part of international application PCT/EP02/04167, filed Apr. 15, 2002 and designating the U.S., which claims priority to U.S. provisional application No. 60/283,345, filed Apr. 13, 2001. The present application also claims priority to German patent application No. DE 102 55 861.2, filed Nov. 29, 2002 and to U.S. provisional application No. 60/430,367, filed Dec. 3, 2002. The present invention relates to the human cellular protein glutathione peroxidase-gastrointestinal (or gastrointestinal glutathione peroxidase, abbreviated GI-GPx) as a potential target for medical intervention against **Hepatitis C virus** (HCV) infections. Furthermore, the present invention relates to a method for the detection of compounds useful for prophylaxis and/or treatment of **Hepatitis C virus** infections and a method for detecting **Hepatitis C virus** infections in an individual or in cells. Also mono- or polyclonal antibodies are disclosed that are effective for the treatment of HCV infections together with methods for treating **Hepatitis C virus** infections or for the regulation of **Hepatitis C virus** production wherein genes or said antibodies may be used. The present invention also relates to chemical compounds and substances which are effective against **Hepatitis C virus** (HCV) infections. In particular, compositions comprising said compounds and/or substances, use of the compounds and/or substances for the preparation of compositions useful for the prophylaxis and/or treatment of HCV infections, as well as methods for preventing and/or treating HCV infections.

  Web site: http://appft1.uspto.gov/netahtml/PTO/search-bool.html

- **Treatment of hepatitis C using hyperthermia**

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  Abstract: The invention provides a method of treating a patient infected with **hepatitis C virus** (HCV) comprising raising the core temperature of the patient and then returning the core temperature of the patient to normal at least one time, wherein the core temperature is raised to a temperature range and a duration sufficient to reduce or eliminate the patient's viral load of HCV.

  Excerpt(s): This invention relates to hyperthermic treatment of hepatitis C. Injected drug users are the largest group of people with hepatitis C infection. People who received a blood transfusion or kidney transplant before a diagnostic test became available form another large group of those infected. Since human immunodeficiency virus (HIV) is also common among injected drug users and is transmitted sexually, about forty percent of HIV infected patients are co-infected with HCV. Various types of HIV such as HIV-1 and HIV-2 exist. **Hepatitis C virus** occurs in six known genotypes and more than fifty subtypes. The **hepatitis C virus** is harbored in the liver and most people infected with HCV eventually will develop cirrhosis or liver carcinoma. HCV can cause an acute or chronic infection. In chronic infection, the infected person can exhibit signs of chronic hepatitis or be a chronic asymptomatic carrier.

  Web site: http://appft1.uspto.gov/netahtml/PTO/search-bool.html

Keeping Current

In order to stay informed about patents and patent applications dealing with hepatitis C virus, you can access the U.S. Patent Office archive via the Internet at the following Web address: **http://www.uspto.gov/patft/index.html**. You will see two broad options: (1) Issued Patent, and (2) Published Applications. To see a list of issued patents, perform the following steps: Under "Issued Patents," click "Quick Search." Then, type "hepatitis C virus" (or synonyms) into the "Term 1" box. After clicking on the search button, scroll down to see the various patents which have been granted to date on hepatitis C virus.

You can also use this procedure to view pending patent applications concerning hepatitis C virus. Simply go back to **http://www.uspto.gov/patft/index.html**. Select "Quick Search" under "Published Applications." Then proceed with the steps listed above.

CHAPTER 6. BOOKS ON HEPATITIS C VIRUS

Overview

This chapter provides bibliographic book references relating to hepatitis C virus. In addition to online booksellers such as **www.amazon.com** and **www.bn.com**, excellent sources for book titles on hepatitis C virus include the Combined Health Information Database and the National Library of Medicine. Your local medical library also may have these titles available for loan.

Book Summaries: Federal Agencies

The Combined Health Information Database collects various book abstracts from a variety of healthcare institutions and federal agencies. To access these summaries, go directly to the following hyperlink: **http://chid.nih.gov/detail/detail.html**. You will need to use the "Detailed Search" option. To find book summaries, use the drop boxes at the bottom of the search page where "You may refine your search by." Select the dates and language you prefer. For the format option, select "Monograph/Book." Now type "hepatitis C virus" (or synonyms) into the "For these words:" box. You should check back periodically with this database which is updated every three months. The following is a typical result when searching for books on hepatitis C virus:

- **Diseases of the Liver and Biliary System, Eleventh Edition**

  Source: Malden, MA: Blackwell Science, Inc. 2002. 706 p.

  Contact: Available from Blackwell Science, Inc. 350 Main Street, Commerce Place, Malden, MA 02148. (800) 215-1000 or (617) 388-8250. Fax (617) 388-8270. E-mail: books@blacksci.com. Website: www.blackwell-science.com. PRICE: $178.95. ISBN: 0632055820.

  Summary: Designed to serve practicing physicians, surgeons and pathologists, as well as clinical students, this textbook presents a comprehensive and up-to-date account of diseases of the liver and biliary system. The text offers 38 chapters: anatomy and function; the assessment of liver function; biopsy of the liver; the hematology of liver disease; ultrasound, computed tomography (CT scan) and magnetic resonance imaging (MRI); hepatocellular failure; hepatic encephalopathy; acute liver failure; ascites (fluid

accumulation); the portal venous system and portal hypertension; the hepatic artery and hepatic vein, and the liver in circulatory failure; jaundice; cholestasis; primary biliary cirrhosis (PBC); sclerosing cholangitis; viral hepatitis, including general features, hepatitis A, hepatitis E, and other viruses; hepatitis B virus and hepatitis Delta virus; **hepatitis C virus;** chronic hepatitis, its general features and autoimmune chronic disease; drugs and the liver; hepatic cirrhosis (scarring); alcohol and the liver; iron overload states; Wilson's disease; nutritional and metabolic liver diseases; the liver in infancy and childhood; the liver in pregnancy; the liver is systemic disease, granulomas, and hepatic trauma; the liver in infections; nodules and benign liver lesions; malignant liver tumors; the role of interventional radiology and endoscopy in imaging of the biliary tract; cysts and congenital biliary abnormalities; gallstones and inflammatory gallbladder diseases; benign stricture of the bile ducts; diseases of the ampulla of Vater and the pancreas; tumors of the gallbladder and bile ducts; and hepatic transplantation. The text includes full-color and black-and-white illustrations and photographs. A detailed subject index concludes the volume.

- **Hepatitis C Handbook**

  Source: Berkeley, CA: North Atlantic Books and Frog, Ltd. 1999. 473 p.

  Contact: Available from North Atlantic Books and Frog, Ltd. P.O. Box 12327, Berkeley, CA 94712. (800) 337-2665 or (510) 559-8277. Fax (510) 559-8279. E-mail: orders@northatlanticbooks.com. Website: www.northatlanticbooks.com. PRICE: $25.00 plus shipping and handling. ISBN: 1556433131.

  Summary: Hepatitis C is a common, recently discovered viral infection usually contracted from the use of intravenous drugs, often decades previously, or less commonly by blood or blood products prior to the introduction of blood screening protocols. This handbook offers an overview of **hepatitis C virus** (HCV) and focuses on the significance of the diagnosis and on lifestyle changes that may prove helpful. The author guides the patient to an informed and balanced choice between the currently available range of treatment options, including interferon and other antiviral agents as well as Chinese herbal remedies. The author hopes to empower readers and so provides detailed medical information about symptoms, lifestyle changes, real life experiences with the disease, and treatment strategies. The first chapter offers facts and figures about the virus and its prevalence; transmission, epidemiology, and the origins of the virus are discussed in Chapter 2, along with professional briefings regarding the prevention of the further proliferation of HCV. Information regarding the various tests that patients are likely to encounter are covered in Chapter 3, together with a discussion of the implications of a diagnosis and whether or not to get tested. Other chapters in the first section cover special situations, including coinfection with other types of hepatitis, children, hemophilia, and Cooley's anemia. The second section offers three chapters that concentrate on the response to having HCV. This section is designed to enable the reader to go through the process of coming to terms with their condition, to better participate as a member of their own health care team, and to deal with members of the medical profession. The third section summarizes the main treatment options open to HCV patients. Chapters cover conventional treatments, traditional Chinese medicine, Western herbal medicine (including medicinal mushrooms), Ayurvedic medicine, vitamins and minerals (and amino acids), homeopathy, miscellaneous treatments, and naturopathy (the 'no treatment' option). The fourth section covers lifestyle options, including diet, alcohol, drugs, exercise, yoga, Qu Gong, and stress management. The final section offers a wealth of resources for readers, including additional technical

information, a glossary, a list of resources, and a subject index. Each chapter also includes references.

- **Management of Hepatitis C: NIH Consensus Development Conference Program and Abstracts**

  Source: Bethesda, MD: National Institutes of Health. 1997. 139 p.

  Contact: Available from NIH Consensus Program Information Center. P.O. Box 2577, Kensington, MD 20891. (888) 644-2667. Fax (301) 816-2494. PRICE: Single copy free.

  Summary: This document presents abstracts of the NIH Consensus Development Conference on the Management of Hepatitis C, held in March 1997 in Bethesda, Maryland. It notes the conference's agenda, panel, speakers, and planning committee members. The document was designed for the use of panelists and participants in the conference and as a pertinent reference document for anyone interested in the conference deliberations. The abstracts are presented in four sections: the natural history of hepatitis C, diagnostic considerations, the epidemiology and spread of hepatitis C, and therapeutic issues. Specific topics covered include the clinical spectrum of disease, blood donors with hepatitis C, hepatitis C and hepatocellular carcinoma (liver cancer), hepatitis C and alcohol, diagnostic tests for hepatitis C, the role of liver biopsy, the epidemiology of hepatitis C, the sexual and perinatal spread of **hepatitis C virus** infection, the use of interferon alfa-2b, ribavirin treatment, drug side effects, predictive factors for a beneficial response to drug therapy in hepatitis C, the treatment of patients with liver cirrhosis, retreatment with interferon, and cost effectiveness considerations. Each abstract includes brief references.

- **Hepatitis C: From Pathogenesis to Prognosis**

  Source: Thousand Oaks, CA: Amgen, Inc. 1997. 32 p.

  Contact: Available from Amgen Professional Services. 1840 DeHavilland Drive, Thousand Oaks, CA 91320-1789. (800) 77-AMGEN. PRICE: Single copy free to health professionals.

  Summary: This document summarizes the current understanding of **hepatitis C virus** (HCV), from its pathogenesis to present research on treatment and cure options. HCV infection results in a chronic disease state in 50 to 70 percent of cases and is now the most common cause of chronic liver disease in the United States. It is highly infectious; known routes of transmission include blood and blood products, injection drug use, and sexual contacts. The virus has been cloned and is now well characterized with respect to both structural and nonstructural proteins. Molecular cloning technology has resulted in the development of specific and sensitive screening, diagnostic, and monitoring assays for HCV. In addition, tests to determine the quantity of viral RNA in blood and to define areas of the viral genome have been developed. Both viral load and genome have been suggested to be predictive of patient response to therapy. Other factors associated with response to treatment include age, presence of iron overload, duration of infection, mode of transmission, and the level of serum bile salts. The development of effective vaccines against hepatitis C is difficult, in part because of the quasispecies nature of HCV. The authors conclude that increased knowledge of the epidemiology and natural history of hepatitis C, coupled with greater understanding of how these diagnostic assays can guide the use of available and future therapies, is crucial in combatting this disease. 8 figures. 4 tables. 53 references. (AA-M).

- **Hepatitis C: Diagnostic Techniques and Monitoring Strategies**

  Source: Thousand Oaks, CA: Amgen, Inc. 1997. 32 p.

  Contact: Available from Amgen Professional Services. 1840 DeHavilland Drive, Thousand Oaks, CA 91320-1789. (800) 77-AMGEN. PRICE: Single copy free to health professionals.

  Summary: This document summarizes the present diagnostic techniques and monitoring strategies used as part of the management of **hepatitis C virus** (HCV). HCV infection results in a chronic disease state in 50 to 70 percent of cases and is now the most common cause of chronic liver disease in the United States. It is highly infectious; known routes of transmission include blood and blood products, injection drug use, and sexual contacts. The virus has been cloned and is now well characterized with respect to both structural and nonstructural proteins. Molecular cloning technology has resulted in the development of specific and sensitive screening, diagnostic, and monitoring assays for HCV. In addition, tests to determine the quantity of viral RNA in blood and to define areas of the viral genome have been developed. Both viral load and genome have been suggested to be predictive of patient response to therapy. The authors review HCV diagnostic and monitoring tests, including liver enzymes, serological assays, virological assays, genotyping and serotyping, and liver biopsy. The discovery of antibodies to HCV or elevated ALT in a patient with or without symptoms of liver disease frequently culminates in the diagnosis of hepatitis C. The sequence of tests used to confirm the diagnosis may depend on the patient's known risk factors and the type of test (ALT, anti-HCV, or both) that initially established the likelihood of infection. The authors conclude that once the diagnosis of HCV infection is confirmed, determination of the presence or absence of cirrhosis, HCV RNA concentration, and genotype or serotype are important predictive factors in determining which patients are most likely to respond to therapy. 8 figures. 8 tables. 66 references. (AA-M).

- **HIV Prophylaxis Following Occupational Exposure**

  Contact: New York Department of Health, AIDS Institute, Room 359, Corning Tower, Albany, NY, 12237, (518) 486-1383.

  Summary: This monograph presents guidelines for post-exposure prophylaxis (PEP) treatment of healthcare workers (HCWs) who have been exposed to the human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS) on the job. It includes the following chapters: (1) Rationale for PEP, (2) Risk Factors Associated with HIV Transmission, (3) Recording Information Following Occupational Exposure, (4) General Management and Considerations, (5) Implementing PEP, (6) Recommended PEP Regimens, (7) Monitoring the HCW Following Occupational Exposure, (8) PEP for the Pregnant HCW, and (9) Occupational Exposure to Hepatitis B Virus and **Hepatitis C Virus.** The appendices include an Informed Consent Form, information on antiretroviral drugs and post-exposure management.

- **The Hepatitis C Handbook**

  Contact: North Atlantic Books, PO Box 12327, Berkeley, CA, 94701-9998, (800) 337-2665, http://www.northatlanticbooks.com.

  Summary: This monograph provides patients and health professionals with detailed information on the epidemiology, diagnosis, and treatment of the **hepatitis C virus** (HCV). This common, recently discovered viral infection affects the liver. Part one presents facts and figures about hepatitis C. Topics include modes of transmission,

epidemiology, natural history, symptoms, diagnostic tests, other types of viral hepatitis, and coinfection with other viruses. Part two focuses on the response to having HCV and offers advice on dealing with members of the medical profession. The third part discusses the main treatment options available to HCV patients, including conventional treatments, traditional Chinese medicine, Western herbal medicine, medicinal mushrooms, Ayurvedic medicine, vitamins, minerals, amino acids, homeopathy, and naturopathy. Part five examines lifestyle adjustment choices available to patients. Topics include diet, alcohol and drug use, exercise, yoga, Qi Gong, and stress. The final part presents additional technical information, a glossary, a list of resources, and an index.

- **Two Patient-Experts Walk You Through Everything You Need to Learn and Do: The First Year: Hepatitis C: An Essential Guide for the Newly Diagnosed**

  Contact: Publishers Group West Incorporated, 1700 4th St, Berkeley, CA, 94710-1711, (510) 528-1444, http://www.pgw.com.

  Summary: This monograph provides people who have **hepatitis C virus** (HCV) infection with up-to-date information on HCV so that they can take an active role in their care. The monograph takes the reader step-by-step through everything they need to do and learn each day of their first week after a diagnosis of HCV, each subsequent week of the first month, and the following 11 months of the year. Each day, week, or month is divided into living and learning sections. The living section focuses on the problem of living with a chronic disease, and the learning section presents facts about the topic being discussed. The monograph begins with advice on coming to terms with the diagnosis. Subsequent chapters deal with taking immediate steps to care for the liver and improve health; discussing one's condition with a partner, other family members, and friends; recognizing symptoms; understanding test results; choosing a physician; making modifications to one's diet and in one's physical activity level; handling sexual and social relationships; doing research; networking with others; and living with coinfection. In addition, the monograph explores both conventional and alternative treatment options, addresses workplace issues, and discusses being an HCV-positive parent or having an HCV-positive child. Throughout the monograph, the personal experiences of others who have HCV are presented.

- **Hepatitis C: Disease Management Guide**

  Contact: Hoffmann-La Roche Incorporated, 340 Kingsland St, Nutley, NJ, 07110, (973) 235-5000, http://www.rocheusa.com.

  Summary: This monograph serves as a guide for managing **hepatitis C virus** (HCV). Section one focuses on current and emerging clinical strategies, diagnosis, and therapeutic drug options. Section two discusses current disease management. Topics include risk factors and transmission, clinical symptoms and signs, serologic tests, diagnosis, and treatment. Section three provides information on various products, including Copegus, Infergen, Intron A for injection, Pegasys, PEG-Intron powder for injection, Rebetol capsules, Rebetol combination therapy, and Roferon-A injection. Section four discusses the meaning of the emerging HCV crisis for pharmacists. Section five presents patient education materials with regard to diagnosis, prevention, screening, and treatment. The final section identifies Internet resources for HCV patients.

- **Hepatitis C: A Personal Guide to Good Health**

  Contact: Publishers Group West Incorporated, 1700 4th St, Berkeley, CA, 94710-1711, (510) 528-1444, http://www.pgw.com.

  Summary: This monograph summarizes and updates existing knowledge about **hepatitis C virus** (HCV) infection. Part one provides information on the discovery of HCV, the features of HCV and other types of hepatitis, the effect of HCV on the liver, modes of transmission, and symptoms. Part two describes the ways HCV is diagnosed, confirmed, and monitored, focusing on blood tests, genotype testing, liver function tests, imaging studies, and liver biopsies. Other topics include the medical and surgical therapies available to treat HCV, including interferon/ribavirin therapy and liver transplantation; alternative and complementary therapies used to treat HCV such as herbs, massage, acupuncture, and other stress-reduction techniques; and the role of diet and exercise in HCV treatment. Part three describes steps individuals can take to assume responsibility for their health. Topics include reaching out for support from physicians, family and friends, coworkers, support groups, professional counselors, and substance abuse specialists as well as stopping the spread of HCV by protecting oneself and others from HCV, supporting efforts to educate others about the dangers of HCV, and advocating for more research.

- **Molecular Biology and Immunology in Hepatology: Advances in the Treatment of Intractable Liver Diseases**

  Source: St. Louis, MO: Elsevier Science. 2002. 362 p.

  Contact: Available from Elsevier Science. Customer Service Department, 11830 Westline Industrial Drive, St. Louis, MO 63146. (800) 545-2522. Fax (800) 535-9935. Email: usbkinfo@elsevier.com. Website: www.elsevierhealth.com. PRICE: $145.00. ISBN: 444506535.

  Summary: This text book offers 25 chapters on intractable liver diseases. Based on the editor's choice of important topics in hepatology, the book ranges from clinical research to basic research, including animal models. Topics include molecular biology and immunology; mechanisms of liver injury in hepatitis B virus (HBV) infection; genetic diversity and pathophysiology of HBV; immunopathogenesis of hepatitis C; interferon therapy for hepatitis C; new therapeutic strategies for chronic hepatitis C; transgenic mouse models for viral hepatitis and the role of hepatitis viruses in the development of liver cancer; gene therapy of viral hepatitis; the reversibility of liver cirrhosis; treatment of liver cancer (hepatocellular carcinoma); gene expression profiles in liver cancer; gene therapy for liver cancer; new immunological treatments for liver cancer; assessment of the reversibility and treatments of alcoholic liver disease; molecular mechanisms of autoimmune hepatitis; roles of **hepatitis C virus** (HCV) in autoimmune hepatitis; molecular mechanisms of T cell responses of autoimmune hepatitis; primary biliary cirrhosis; overlap syndrome; etiology and pathophysiology of fulminant hepatic failure; cytokines and fulminant hepatic failure; treatment and prognosis of fulminant hepatic failure; living related liver transplantation; viral cirrhosis and liver cancer in relation to living donor liver transplants. Each chapter concludes with references; the text concludes with a subject index.

- **Viral Hepatitis: Diagnosis, Treatment, Prevention**

  Source: New York, NY: Marcel Dekker, Inc. 1997. 532 p.

Contact: Available from Marcel Dekker, Inc. 270 Madison Avenue, New York, NY 10016. (212) 696-9000. Fax (212) 685-4540. PRICE: $175.00. ISBN: 0824794168.

Summary: This text familiarizes readers with current methods of diagnosis, treatment, and prevention of human viral hepatitis. Sixteen chapters cover: methods and applications of molecular diagnostic testing for viral hepatitis; the hepatitis A virus; the molecular biology and immunopathology of the hepatitis B virus; the prevention and therapy of clinical disease arising from the hepatitis B virus; the **hepatitis C virus;** the hepatitis D virus; the epidemiology and biology of the hepatitis E virus; other hepatitis viruses including the hepatitis G virus; the role of hepatitis viruses in acute liver failure; hepatocellular carcinoma and viral hepatitis; extrahepatic manifestations of chronic viral hepatitis; the overlap of chronic viral hepatitis and autoimmune hepatitis; liver transplantation and viral hepatitis B, D, and C; viral hepatitis in marrow and stem-cell transplant patients; viral hepatitis in the immunocompromised host; and the role of iron in chronic viral hepatitis. The authors evaluate diagnostic serological techniques such as ELISAs and PCRs; highlight nonhuman primate and transgenically created animal models used in disease transmission studies, virus isolation, and serological assays and vaccine development; review the management of fulminant hepatic failure and hepatitis in the immunocompromised patient; discuss how diagnosis may be complicated by predominant extrahepatic manifestations; assess various vaccines recent licensing and future prospects; and appraise the cost effectiveness of medical treatments with antiviral agents, the role of liver transplantation, and preventive measures. Each chapter includes extensive references, and a subject index concludes the volume.

Chapters on Hepatitis C Virus

In order to find chapters that specifically relate to hepatitis C virus, an excellent source of abstracts is the Combined Health Information Database. You will need to limit your search to book chapters and hepatitis C virus using the "Detailed Search" option. Go to the following hyperlink: **http://chid.nih.gov/detail/detail.html**. To find book chapters, use the drop boxes at the bottom of the search page where "You may refine your search by." Select the dates and language you prefer, and the format option "Book Chapter." Type "hepatitis C virus" (or synonyms) into the "For these words:" box. The following is a typical result when searching for book chapters on hepatitis C virus:

- **Alcoholic Liver Diseases**

  Source: in Textbook of Gastroenterology. 4th ed. [2-volume set]. Hagerstown, MD: Lippincott Williams and Wilkins. 2003. p. 2415-2436.

  Contact: Available from Lippincott Williams and Wilkins. P.O. Box 1600, Hagerstown, MD 21741. (800) 638-6423. Fax: (301) 223-2400. Website: www.lww.com. PRICE: $289.00. ISBN: 781728614.

  Summary: Alcoholic liver disease (ALD) continues to be a major cause of cirrhosis (liver scarring) and death around the world. This chapter on ALD is from a comprehensive gastroenterology textbook that provides an encyclopedic discussion of virtually all the disease states encountered in a gastroenterology practice. In this chapter, the authors cover epidemiology, pathogenesis, clinical manifestations, differential diagnosis, course and complications, and treatment strategies. Specific topics include the metabolism of ethanol, the nutritional aspects of ALD, genetic predisposition to alcoholism and ALD, the genesis and consequences of fatty liver, the roles of oxidant stress, the role of protein

adduct formation, cytoskeletal changes in ALD, the role of lipopolysaccharide and the Kupffer cells, pathways of hepatic stellate cell activation, gender differences in the response to alcohol, apoptosis in ALD, alcoholic fatty liver, alcoholic hepatitis, alcoholic cirrhosis, **hepatitis C virus** and ALD, hepatic iron stores and ALD, and complications of alcoholism and ALD, including metabolic disorders, infections, altered neurological status, kidney dysfunction, and worsening liver disease. The chapter is illustrated with black-and-white graphs and drawings. 3 figures. 6 tables. 225 references.

- **What Is Hepatitis C?: An Introduction**

  Source: in Everson, G.T. and Weinberg, H. Living with Hepatitis C: A Survivor's Guide. New York, NY: Hatherleigh Press. 1999. p. 1-14.

  Contact: Available from Hatherleigh Company, Ltd. 1114 First Avenue, Suite 500, New York, NY 10021. (800) 367-2550 or (212) 832-1039. Website: hatherleigh.com. PRICE: $14.95 plus shipping and handling. ISBN: 1578260345.

  Summary: Hepatitis C is a viral infection that causes inflammation, injury, and ultimately scarring of the liver (cirrhosis). This chapter introducing hepatitis C is from a book that offers information and guidance for people living with hepatitis C. The authors explain in nontechnical language some basic facts and statistics about hepatitis C, its history and discovery, and information about viruses and other forms of viral hepatitis. Hepatitis C is primarily a blood to blood virus, so loved ones cannot easily be infected by the patient with hepatitis C. However, hepatitis C can put a heavy strain on relationships. The authors portray the **hepatitis C virus** as a slow moving time bomb that can lurk in the liver for decades, silently injuring the liver and setting the stage for complications. The earlier the diagnosis, the better the choices that are available for long term care and supportive measures such as good nutrition. The chapter concludes with information about research into a potential cure for hepatitis C. The chapter includes lengthy quotes from patients with hepatitis, which offer the patients' perspectives, insights, and experiences to the reader. 1 figure. 1 reference.

- **Hepatocellular Carcinoma**

  Source: in Textbook of Gastroenterology. 4th ed. [2-volume set]. Hagerstown, MD: Lippincott Williams and Wilkins. 2003. p. 2491-2512.

  Contact: Available from Lippincott Williams and Wilkins. P.O. Box 1600, Hagerstown, MD 21741. (800) 638-6423. Fax: (301) 223-2400. Website: www.lww.com. PRICE: $289.00. ISBN: 781728614.

  Summary: Hepatocellular carcinoma (HCC, liver cancer) is the fifth most common cancer and the third most frequent cause of cancer death worldwide, with an estimated 560,000 new cases per year. There are strong etiologic (causative) associations with chronic hepatitis B virus, chronic **hepatitis C virus,** alcoholic cirrhosis, other causes of chronic liver disease, and dietary aflatoxin exposure. This chapter on HCC is from a comprehensive gastroenterology textbook that provides an encyclopedic discussion of virtually all the disease states encountered in a gastroenterology practice. In this chapter, the authors cover epidemiology, etiology and risk factors, pathogenesis, surveillance, differential diagnosis, diagnosis, staging, locoregional therapies, and systemic therapy. The authors conclude that the selection of an appropriate treatment strategy for patients with HCC depends on careful tumor staging and assessment of the underlying liver disease. All patients with localized HCC should be evaluated for the potentially curative therapy options of partial hepatectomy or liver transplantation. Given the lack of efficacy data, there are no proven systemic chemotherapy regimens,

immunotherapy approaches, or hormonal therapies that can be recommended at this time. The chapter is illustrated with black-and-white graphs and drawings. 9 figures. 4 tables. 165 references.

- **Hepatic Tumors**

  Source: in Friedman, L.S. and Keeffe, E.B., eds. Handbook of Liver Disease. Philadelphia, PA: Churchill-Livingstone. 1998. p. 361-371.

  Contact: Available from W.B. Saunders Company. Book Order Fulfillment Department, 6277 Sea Harbor Drive, Orlando, FL 32887-4430. (800) 545-2522. Fax (800) 874-6418. E-mail: wbsbcs@harcourtbrace.com. PRICE: $73.00 plus shipping and handling. ISBN: 0443055203.

  Summary: This chapter on hepatic tumors (benign and malignant) is from a comprehensive handbook in outline format that offers easy access to information on the full range of liver disorders and covers symptoms, signs, differential diagnoses, and treatments. Hemangioma of the liver is found in up to 1 percent of the normal population and is rarely of clinical consequence. Other benign tumors of the liver, including hepatic adenoma, are rare. Hepatic adenoma usually requires surgical resection because of the risks of rupture and the development of malignancy. In the presence of cirrhosis, hepatocellular carcinoma (HCC) accounts for approximately 75 percent of all liver tumors. The most important risk factors for development of HCC are cirrhosis and chronic hepatitis B virus, and **hepatitis C virus** infection. Although surgical resection or liver transplantation offers the best chance of curing HCC, few patients are suitable for surgery. Cholangiocarcinoma (CCC) is not usually associated with cirrhosis; CCC of the central type is often associated with primary sclerosing cholangitis and has a poor prognosis. 3 figures. 4 tables. 10 references. (AA-M).

- **Hepatitis C Virology: Antigen, Antibody, and Molecular Testing**

  Source: in Gordon, S.C. Management of Chronic Viral Hepatitis. New York, NY: Marcel Dekker Inc. 2002. p. 33-64.

  Contact: Available from Marcel Dekker, Inc. 270 Madison Avenue, New York, NY 10016. (212) 696-9000. Fax (212) 685-4540. Website: www.dekker.com. PRICE: $150.00 plus shipping and handling. ISBN: 0824705823.

  Summary: This chapter on hepatitis B virology is from a monograph on the management of chronic viral hepatitis (liver inflammation), bringing the advances of clinical and basic research into the doctor's office. This chapter uses a brief clinical case presentation in order to address the real life intricacies of managing patients who present with viral hepatitis. The authors focus on antigen, antibody, and molecular testing for hepatitis C virology. The case patient is a 54 year old male physician with a history of acute myelogenous leukemia who received multiple transfusions in August 1989 who developed abnormal liver chemistries in March 1990. Serological (blood) testing revealed that he was anti-HCV negative by the ELISA 1 assay; anti-HAV (total) was positive, but anti HAV IgM was negative. HBsAg and anti HBc were negative and anti HBs positive. Both the antinuclear antibodies (ANA) and the anti smooth muscle antibody tests were negative. This case illustrates a number of points that relate to the history of the **hepatitis C virus** and its associated serological assays. The first generation test for anti HCV was released in the United States in May 1990, although it was available in Europe as early as 1989. This patient had hepatitis C in 1990, but it was not until later with the development of more refined assays that his serological profile became defined. Later, as the patient underwent treatment with antiviral agents, the

development of increasingly more sophisticated molecular based assays assisted in his clinical management. 11 figures. 2 tables. 53 references.

- **Persistently Normal Alanine Aminotransferase Levels in Individuals with Hepatitis C**

  Source: in Gordon, S.C. Management of Chronic Viral Hepatitis. New York, NY: Marcel Dekker Inc. 2002. p. 217-232.

  Contact: Available from Marcel Dekker, Inc. 270 Madison Avenue, New York, NY 10016. (212) 696-9000. Fax (212) 685-4540. Website: www.dekker.com. PRICE: $150.00 plus shipping and handling. ISBN: 0824705823.

  Summary: This chapter on persistently normal alanine aminotransferase (ALT) levels in individuals with hepatitis C is from a monograph on the management of chronic viral hepatitis (liver inflammation), bringing the advances of clinical and basic research into the doctor's office. Initial treatment protocols for **hepatitis C virus** (HCV) used criteria for study enrollment based on recommendations for hepatitis B; that is, patients with elevated ALT levels. In addition, many patients with normal ALT were initially not even suspected to be infected with HCV. The authors note that the concept of the 'healthy carrier' of HCV should be dispelled. Still in question is why some patients have ALT which remains persistently normal. Although advances have been made in understanding this cohort, questions remain regarding histology, natural history, viral levels, and genotypes as well as response to therapy in patients with persistently normal ALT. To date, there is no compelling evidence that patients with persistently normal ALT are significantly different from patients with abnormal ALT. Nevertheless, the treatment of individuals with hepatitis C viremia and normal ALT has not been formally recommended. Longer treatment trials with larger numbers of patients using combination therapy and newer antivirals are necessary before definitive recommendations regarding the proper therapy of this unique cohort of hepatitis C infected patients can be made. 1 table. 29 references.

- **Current Treatment of Hepatitis C**

  Source: in Gordon, S.C. Management of Chronic Viral Hepatitis. New York, NY: Marcel Dekker Inc. 2002. p. 187-216.

  Contact: Available from Marcel Dekker, Inc. 270 Madison Avenue, New York, NY 10016. (212) 696-9000. Fax (212) 685-4540. Website: www.dekker.com. PRICE: $150.00 plus shipping and handling. ISBN: 0824705823.

  Summary: This chapter on the current treatment of hepatitis C is from a monograph on the management of chronic viral hepatitis (liver inflammation), bringing the advances of clinical and basic research into the doctor's office. Two brief case presentations to address the real life intricacies of managing patients who present with viral hepatitis. Approximately 20 to 30 percent of patients infected with **hepatitis C virus** (HCV) will develop cirrhosis (liver scarring) and are at risk for developing complications of end stage liver disease, including hepatocellular carcinoma (HCC, liver cancer). Chronic hepatitis C is now the most common indication for liver transplantation in the United States. Thus, there is a need for effective therapies to treat HCV infection. For initial treatment of patients with hepatitis C, the most effective therapy in terms of biochemical, virological, and histological response criteria is the combination of interferon (IFN) and ribavirin. The duration of this therapy should be based on HCV genotype, with 48 weeks of therapy for patients with type 1 genotype and 24 weeks of therapy for other genotypes. Patients who are not candidates for IFN plus ribavirin

combination therapy can be considered for IFN monotherapy. Side effects and the need for dosage modification or discontinuation are more frequent with IFN plus ribavirin compared to IFN monotherapy, but these can usually be managed with close follow up and careful monitoring. 3 figures. 6 tables. 73 references.

- **Retreatment of Hepatitis C: Interferon Nonresponders**

  Source: in Gordon, S.C. Management of Chronic Viral Hepatitis. New York, NY: Marcel Dekker Inc. 2002. p. 233-261.

  Contact: Available from Marcel Dekker, Inc. 270 Madison Avenue, New York, NY 10016. (212) 696-9000. Fax (212) 685-4540. Website: www.dekker.com. PRICE: $150.00 plus shipping and handling. ISBN: 0824705823.

  Summary: This chapter on the retreatment of hepatitis C patients who have not responded to interferon (IFN) therapy is from a monograph on the management of chronic viral hepatitis (liver inflammation), bringing the advances of clinical and basic research into the doctor's office. This chapter uses a brief clinical case presentation in order to address the real life intricacies of managing patients who present with viral hepatitis. The case patient is a 49 year old man who was diagnosed with subclinical chronic **hepatitis C virus** (HCV) infection. The patient received interferon therapy and tolerated it well, with minimal adverse effects. However, viral titer, after 3 months on interferon monotherapy, showed persistence of the HCV. He was considered a nonresponder and interferon therapy was discontinued. Additional treatments, including a longer course of interferons and a course of combination therapy with interferon and ribavirin, were undertaken. There was no substantial change in viral titer, although slight improvement in aminotransferase (ALT) levels was seen. The author discusses retreatment with alternative forms of interferon, and using adjunctive therapy, including iron reduction therapy, amantadine and rimantadine, ursodeoxychlic acid (UDCA), and nonsteroidal antiinflammatory drugs (NSAIDs). 4 tables. 92 references.

- **Hepatitis C: An Overview**

  Source: in Coggins, C.H., et al, eds. Annual Review of Medicine: Selected Topics in the Clinical Sciences. Palo Alto, CA: Annual Review, Inc. 1995. Volume 46: 309-317.

  Contact: Available from Annual Reviews, Inc. 4139 El Camino Way, P.O. Box 10139, Palo Alto, CA 94303. (800) 347-8007 or (415) 259-5017 for reprints of individual articles; (800) 523-8635 for subscriptions. E-mail apr@class.org. PRICE: $47 including shipping and handling. ISBN: 0824305450. ISSN: 0066-4219.

  Summary: This entry from the Annual Review of Medicine provides readers with an overview of **hepatitis C virus** (HCV). Topics include structure and genotypes; diagnostic tests; epidemiology; HCV related hepatitis and cirrhosis; HCV associated hepatocellular carcinoma; treatment options, including the use of interferon and liver transplantation; and HCV vaccines. 1 figure. 41 references.

- **Treatments in Development**

  Source: in Green, W.F. First Year: Hepatitis B. New York, NY: Marlowe and Company. 2002. p. 183-190.

  Contact: Available from Marlowe and Company. 161 William Street, 16th Floor, New York, NY 10038. PRICE: $15.95 plus shipping and handling. ISBN: 1569245339.

Summary: Viral hepatitis B (liver infection) is one of the most preventable medical conditions due to the availability of a hepatitis B vaccine, yet an estimated 100,000 people in the United States are infected each year, and 6,000 die from complications. When the author of this book was diagnosed in 1993, he decided to be proactive in his quest to understand and manage his illness. In this chapter, the author focuses on what readers might be learning about by the seventh month after they receive their diagnosis of hepatitis B virus (HBV) infection, discussing treatments in development. In nontechnical language, the author discusses drugs that are currently in Phase III trials, including nucleotide analogues and immune system enhancers; nonnucleoside antivirals; and gene and stem-cell therapies. A second section of the chapter addresses co-infection with HBV and other diseases, including **hepatitis C virus** (HCV), hepatitis D virus (HDV), HIV, and liver cancer. Readers are encouraged to learn as much as they can about new treatment options that may be available.

- **Acute Viral Hepatitis**

  Source: in Brandt, L., et al., eds. Clinical Practice of Gastroenterology. Volume Two. Philadelphia, PA: Current Medicine. 1999. p. 831-839.

  Contact: Available from W.B. Saunders Company. Order Fulfillment, 6277 Sea Harbor Drive, Orlando, FL 32887. (800) 545-2522. Fax (800) 874-6418 or (407) 352-3445. Website: www.wbsaunders.com. PRICE: $235.00 plus shipping and handling. ISBN: 0443065209 (two volume set); 0443065217 (volume 1); 0443065225 (volume 2).

  Summary: Viral infection is the most common cause of acute and chronic liver disease in the world. This chapter on acute viral hepatitis (liver infection) is from a lengthy textbook that brings practitioners up to date on the complexities of gastroenterology practice, focusing on the essentials of patient care. The author notes that the spectrum of clinical illness due to hepatitis infection is extraordinarily broad. In many patients, infection is asymptomatic and entirely subclinical; in others, acute, life threatening liver failure may occur. At present, there is no specific, effective treatment for acute viral hepatitis with the exception of liver transplant for patients with acute irreversible liver failure. Hepatitis viruses are classified into two distinct groups: the enterically transmitted (through the digestive tract), nonenveloped agents, including hepatitis A virus (HAV) and hepatitis E virus (HEV); and the bloodborne, enveloped agents, including hepatitis B virus (HBV), hepatitis D virus (HDV), and **hepatitis C virus** (HCV). A fourth bloodborne agent, the hepatitis G virus (HGV) appears unlikely to be a true hepatitis virus and is not covered in this chapter. The enterically transmitted hepatitis viruses survive exposure to bile, are shed in feces, and produce infections that are generally self limited although they may cause severe hepatitis and acute liver failure; chronic disease is not seen. In contrast, the bloodborne enveloped hepatitis viruses are disrupted by exposure to bile or detergents, are not shed in feces, and may be associated with prolonged viremia (presence of the virus in the blood), persistent infectivity, and progression to chronic liver disease. Effective and safe vaccines are available for immunoprophylaxis against HAV and HBV infections (the latter vaccine also prevents HDV infection). Immunoprophylaxis against infection with other hepatitis viruses is not currently available. 10 figures. 4 tables. 21 references.

CHAPTER 7. MULTIMEDIA ON HEPATITIS C VIRUS

Overview

In this chapter, we show you how to keep current on multimedia sources of information on hepatitis C virus. We start with sources that have been summarized by federal agencies, and then show you how to find bibliographic information catalogued by the National Library of Medicine.

Video Recordings

An excellent source of multimedia information on hepatitis C virus is the Combined Health Information Database. You will need to limit your search to "Videorecording" and "hepatitis C virus" using the "Detailed Search" option. Go directly to the following hyperlink: **http://chid.nih.gov/detail/detail.html**. To find video productions, use the drop boxes at the bottom of the search page where "You may refine your search by." Select the dates and language you prefer, and the format option "Videorecording (videotape, videocassette, etc.)." Type "hepatitis C virus" (or synonyms) into the "For these words:" box. The following is a typical result when searching for video recordings on hepatitis C virus:

- **Hepatitis C: A Viral Mystery**

  Source: Boston, MA: Fanlight Productions. 2000. (videocassette).

  Contact: Available from Fanlight Productions. 4196 Washington Street, Boston, MA 02131. (800) 937-4113 or (617) 469-4999. Fax (617) 469-3379. E-mail: fanlight@fanlight.com. Website: www.fanlight.com. PRICE: $195.00 plus shipping and handling.

  Summary: Hepatitis C is a viral disease of the liver which affects nearly four million Americans. The virus is primarily spread through blood contamination. There is no vaccine and no definite cure for the infection. This documentary videotape profiles several individuals who are living with this serious, chronic illness. In addition to discussing the available medical treatments, the program explores alternative options for treatment, including dietary changes, herbal therapies, meditation, guided imagery, and Qi Gong. The program reviews the modes of transmission of **hepatitis C virus**

(HCV), including through blood transfusions, IV drug use, unsafe sex practices or multiple sexual partners, and tattooing and body piercing. The program interviews Dr. Stephen Steady, a hepatologist (liver specialist) who reminds viewers that many people with HCV infections are asymptomatic, but complications can be rampant, affecting other organ systems and overall quality of life (primarily through fatigue). The program reviews the drug therapy options (interferon and ribavirin, predominantly), noting that these treatments are effective only in 40 percent of the patients with hepatitis C, yet they can cause many side effects of their own. The program concludes with a look at the need for liver transplantation for some patients with hepatitis C, the important role of hepatitis C education for prevention, and support groups for patients with the illness.

- **Hepatitis C: The Silent Scourge**

  Source: Princeton, NJ: Films for the Humanities and Sciences. 1996. (videocassette).

  Contact: Available from Films for the Humanities and Sciences. P.O. Box 2053, Princeton, NJ 08543-2053. (800) 257-5126 or (609) 275-1400. Fax (609) 275-3767. E-mail: custserv@films.com. Website: www.films.com. PRICE: $99.00 plus shipping and handling. Order number CAF6419.

  Summary: Hepatitis C virus (HCV) is a disease that is transmitted primarily by contact with infected blood and that manifests few symptoms. As many as 3.5 million people in the United States are believed to carry the virus, and many are not even aware that they have been exposed; 10,000 die from it each year. This program, hosted by Drs. Miriam Alter and Harold Margolis of the Centers for Disease Control and Prevention (CDC), explains current knowledge about the newest strain of the hepatitis virus, and its causes, treatment, and prevention. The program is designed like a news report and begins with an overview of the role and functions of the liver. The program then reviews the various forms of the hepatitis virus, noting that all of them cause liver inflammation and cirrhosis and can lead to symptoms like the flu, dark urine, or jaundice (yellowing of the skin). The narrators review the ways each type is transmitted, the symptoms, the treatment and side effects, prognostic factors, the availability of immunization, and risk factors. The program goes into more depth on hepatitis C, interviewing patients and health care providers. A brief section describes the use of liver transplantation as the final option for end stage liver failure caused by hepatitis. Another section interviews Thelma King Theil, the chair of the Hepatitis Foundation International, who focuses on the activities of the organization, particularly those related to prevention.

- **Fighting Hepatitis C**

  Source: Princeton, NJ: Films for the Humanities and Sciences. 2001. (videorecording).

  Contact: Available from Films for the Humanities and Sciences. PO Box 2053, Princeton, NJ 08543-2053. (800) 257-5126. Fax: (609) 275-3767. Email: custserv@films.com. Website: www.films.com. PRICE: $129.95; plus shipping and handling. Item number: BVL30008.

  Summary: Hepatitis C virus is the most common chronic bloodborne disease in America, and the number one reason for liver transplants. This video program from The Doctor Is In series features Raymond Koff, of the University of Massachusetts Medical School, and Kris Kowdley, of the University of Washington School of Medicine. The program emphasizes the need for early testing and treatment of hepatitis C. The program includes interviews with hepatitis C patients, including a woman who cites her youthful experimentation with injected drugs as the cause of her infection.

- **Hepatitis C: Diagnosis, Clinical Management, and Prevention**

  Source: Cedar Grove, NJ: Hepatitis Foundation International. November 22, 1997. (videocassette, audiocassette, manual).

  Contact: Available from Hepatitis Foundation International. 30 Sunrise Terrace, Cedar Grove, NJ 07009. (800) 891-0707. PRICE: $15.00 each for videotape and reference text; $10.00 for audiocassette tape.

  Summary: These materials on hepatitis C are from a satellite video conference sponsored by the Hepatitis Foundation International and the Centers for Disease Control and Prevention. The packet includes a videotape of the conference itself, an audiotape of the discussions from the conference, and the accompanying reference manual. The program featured speakers on eight topics: burden and prevalence, risk factors and epidemiology, serology, chronic hepatitis C infection in children, followup laboratory tests and clinical evaluation, the natural history of **hepatitis C virus** infection, treatment, and counseling messages. One case study is also presented. The slides from the program are reproduced in the manual. The manual includes a section on risk assessment with examples of questions to identify patients at risk for HCV infection and to determine whether serologic testing may be indicated. Screening recommendations for HCV infection are provided in chart format. An additional section compiles some concerns expressed by patients diagnosed with hepatitis C. The manual concludes with a reprint of the 1997 National Institutes of Health Consensus Statement and an article on advising patients who seek alternative medical therapies such as chiropractic, acupuncture, homeopathy, and herbal remedies. Additional handouts to stimulate and support physician patient communication are provided, as well as a list of resources noting organizations that can provide patients with information on hepatitis. The manual is spiral bound.

- **Hepatitis C: The Silent Epidemic**

  Contact: Aquarius Health Care Videos, Olde Medfield Sq, 266 Main St Ste 33B, Medfield, MA, 02052-2099, (888) 440-2963, http://www.aquariusproductions.com.

  Summary: This video presents information about the sexually transmitted disease (STD), hepatitis C. The video explains why injection drug users (IDUs) are at greater risk for hepatitis C. It explains diagnosis, symptoms, transmission, treatment, side effects of the treatment, lifestyle problems that are the result of addiction to chemical substances, and what individuals must do to take care of themselves and stay healthy. The information in the video is presented by a hepatologist and five people who are living with the **hepatitis C virus.**

- **Respect Yourself : Protect Yourself : Teens Talk to Teens About Liver Wellness**

  Contact: Hepatitis Foundation International, 30 Sunrise Terr, Cedar Grove, NJ, 07009, (800) 857-0707.

  Summary: This video, designed for adolescents, discusses the hepatitis B virus (HBV) and the **hepatitis C virus** (HCV) and their effects on the liver. The video explains the functions of the liver and states that the liver is a 'non-complaining' organ, meaning that most disorders that affect it are asymptomatic. The video recommends vaccination to help prevent HBV. For HBV and HCV prevention, it advises the viewers to avoid sharing any items that might contain or carry blood such as razors or injection drug needles and other paraphernalia.

- **Bloodborne Pathogens 2000**

  Contact: Long Island Productions, 106 Capitola Dr, Durham, NC, 27713-4471, (919) 544-6663, http://www.lip-online.com.

  Summary: This videocassette provides information about bloodborne pathogens, including the human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS), the hepatitis B virus (HBV), and the **hepatitis C virus** (HCV), and how they can be prevented in the workplace. Occupational exposures to bloodborne pathogens usually occur when a worker comes into direct contact with infected bodily fluids and tissues. HIV is an infection that weakens the immune system and develops into AIDS, whereas HBV and HCV infect the liver. HBV is the most common occupational hazard among health professionals and can be prevented with a vaccine. The video lists the body fluids that can carry HIV, HBV, and HCV. Universal precautions can help to protect health and safety workers from occupational exposures to bloodborne pathogens and include measures such as the use of personal protective equipment (PPE), proper hygiene, and sanitation. Instructions are provided about how to wear and remove gloves and handle sharps containers as well as other biohazard disposal/storage materials. The video discusses the occupational risks for the transmission of a bloodborne pathogen and the procedures that should be followed immediately after an accidental exposure has occurred.

- **Emergency Medical Update: Bloodborne Pathogens**

  Contact: Lockert - Jackson and Associates, PO Box 11380, Winslow, WA, 98110-5380, (206) 842-8454.

  Summary: This videorecording is designed to educate and train emergency medical technicians (EMT's) about the Occupational Safety and Health Administration's (OSHA's) bloodborne pathogen standards and guidelines. Bloodborne pathogens include hepatitis B virus, **hepatitis C virus,** HIV, and syphilis. Every time an individual treats a patient, risks are taken. It is important to review the agency's exposure-control plan, including specific information on personal protective equipment, disposal and decontamination, hepatitis B vaccinations, and warning signs used to identify contaminated materials. A post-exposure followup is also necessary. The videorecording includes three tracks titled, On the Run; Bloodborne Pathogen Exposure, On the Run: Exposure Control - A Part of Every Call, and Take Care: Post Exposure Follow Up.

- **Hepatitis C: Unknown Epidemic**

  Source: Princeton, NJ: Films for the Humanities and Sciences. 1998. (videocassette).

  Contact: Available from Films for the Humanities and Sciences. P.O. Box 2053, Princeton, NJ 08543-2053. (800) 257-5126 or (609) 275-1400. Fax (609) 275-3767. E-mail: custserv@films.com. Website: www.films.com. PRICE: $99.00 to purchase; $75.00 for rental; plus shipping and handling. Order number BVL9342.

  Summary: This videotape offers a segment of ABC's Nightline program that explores the epidemic of **hepatitis C virus** (HCV) infection in the United States. In this program, ABC News anchor Forrest Sawyer investigates the virus with Dr. Miriam Alter, epidemiologist at the Centers for Disease Control and Prevention; Dr. Jerome Groopman, professor at Harvard Medical School; and Andi Thomas, founder of the advocacy group Hep-C ALERT. Together they examine topics including risk factors associated with the disease, improvements in blood screening, the results of targeted

looks back at past blood recipients, and the need for additional funding to increase research. Hepatitis C is characterized as a definite health epidemic: 15 percent of the people who get infected successfully fight it off; in 80 percent of those infected, the disease becomes chronic; and in 5 percent of those infected, HCV results in liver cirrhosis (scar tissue), which can then lead to cancer and death. It is virtually impossible to predict who will be in which category. The disease is spread predominantly through needle sharing, sexual contact, and blood transfusions occurring prior to the 1990's. The disease has been called the silent epidemic because it was only identified 10 years ago and the infection remains symptomless for decades. The three panelists interviewed share their information and differences of opinions on the wisdom of getting tested for HCV, the magnitude of the public health problem of the disease, the need for targeted look back for people who received blood transfusions, and the emotions of dealing with the disease.

- **Update on Management of Hepatitis C**

  Source: Kansas City, MO: American Academy of Family Physicians. 2000. (videocassette).

  Contact: Available from American Academy of Family Physicians. 8880 Ward Parkway, Kansas City, MO 64114-2797. (800) 274-2237. PRICE: $17.95 for members; $25.00 for non-members, plus shipping and handling.

  Summary: Viral hepatitis remains the most common cause of liver disease worldwide and infection with the **hepatitis C virus** (HCV) has become a serious health problem in the United States. This continuing education program assists family physicians in this new challenge of the identification and diagnosis of patients at greatest risk of HCV infection. While there is, as yet, no known cure for HCV, early medical intervention and lifestyle changes can significantly improve the prognosis. Infection with HCV can lead to chronic hepatitis, cirrhosis (liver scarring), and hepatocellular carcinoma (HCC, liver cancer). Unlike hepatitis A and B, there is no vaccination available to prevent hepatitis C, nor are there any preexposure or postexposure prophylaxis (prevention) options. This program reviews the epidemiology of HCV, identification of patients at risk, diagnosis, HCV related liver disease, and management approaches, including interferon monotherapy, combination therapy, side effects, contraindications, and ongoing medical monitoring. The program includes a video tape and a study guide; the latter includes references and a patient education handout, as well as a posttest with which viewers can qualify for continuing education credit. 6 figures. 13 tables. 31 references.

CHAPTER 8. PERIODICALS AND NEWS ON HEPATITIS C VIRUS

Overview

In this chapter, we suggest a number of news sources and present various periodicals that cover hepatitis C virus.

News Services and Press Releases

One of the simplest ways of tracking press releases on hepatitis C virus is to search the news wires. In the following sample of sources, we will briefly describe how to access each service. These services only post recent news intended for public viewing.

PR Newswire

To access the PR Newswire archive, simply go to **http://www.prnewswire.com/**. Select your country. Type "hepatitis C virus" (or synonyms) into the search box. You will automatically receive information on relevant news releases posted within the last 30 days. The search results are shown by order of relevance.

Reuters Health

The Reuters' Medical News and Health eLine databases can be very useful in exploring news archives relating to hepatitis C virus. While some of the listed articles are free to view, others are available for purchase for a nominal fee. To access this archive, go to **http://www.reutershealth.com/en/index.html** and search by "hepatitis C virus" (or synonyms). The following was recently listed in this archive for hepatitis C virus:

- **Alcohol ups hepatitis C virus replication**
  Source: Reuters Health eLine
  Date: July 22, 2003

- **Alcohol enhances hepatitis C virus replicon expression**
  Source: Reuters Medical News
  Date: July 22, 2003
- **Genetic variability of hepatitis C virus may influence treatment outcome**
  Source: Reuters Medical News
  Date: May 26, 2003

The NIH

Within MEDLINEplus, the NIH has made an agreement with the New York Times Syndicate, the AP News Service, and Reuters to deliver news that can be browsed by the public. Search news releases at **http://www.nlm.nih.gov/medlineplus/alphanews_a.html**. MEDLINEplus allows you to browse across an alphabetical index. Or you can search by date at the following Web page: **http://www.nlm.nih.gov/medlineplus/newsbydate.html**. Often, news items are indexed by MEDLINEplus within its search engine.

Business Wire

Business Wire is similar to PR Newswire. To access this archive, simply go to **http://www.businesswire.com/**. You can scan the news by industry category or company name.

Market Wire

Market Wire is more focused on technology than the other wires. To browse the latest press releases by topic, such as alternative medicine, biotechnology, fitness, healthcare, legal, nutrition, and pharmaceuticals, access Market Wire's Medical/Health channel at **http://www.marketwire.com/mw/release_index?channel=MedicalHealth**. Or simply go to Market Wire's home page at **http://www.marketwire.com/mw/home**, type "hepatitis C virus" (or synonyms) into the search box, and click on "Search News." As this service is technology oriented, you may wish to use it when searching for press releases covering diagnostic procedures or tests.

Search Engines

Medical news is also available in the news sections of commercial Internet search engines. See the health news page at Yahoo (**http://dir.yahoo.com/Health/News_and_Media/**), or you can use this Web site's general news search page at **http://news.yahoo.com/**. Type in "hepatitis C virus" (or synonyms). If you know the name of a company that is relevant to hepatitis C virus, you can go to any stock trading Web site (such as **http://www.etrade.com/**) and search for the company name there. News items across various news sources are reported on indicated hyperlinks. Google offers a similar service at **http://news.google.com/**.

BBC

Covering news from a more European perspective, the British Broadcasting Corporation (BBC) allows the public free access to their news archive located at **http://www.bbc.co.uk/**. Search by "hepatitis C virus" (or synonyms).

Newsletter Articles

Use the Combined Health Information Database, and limit your search criteria to "newsletter articles." Again, you will need to use the "Detailed Search" option. Go directly to the following hyperlink: **http://chid.nih.gov/detail/detail.html**. Go to the bottom of the search page where "You may refine your search by." Select the dates and language that you prefer. For the format option, select "Newsletter Article." Type "hepatitis C virus" (or synonyms) into the "For these words:" box. You should check back periodically with this database as it is updated every three months. The following is a typical result when searching for newsletter articles on hepatitis C virus:

- **Research Agenda for Viral Hepatitis (editorial)**

  Source: Liver Update. 9(2): 1-2. Fall 1995.

  Contact: Available from American Liver Foundation. 1425 Pompton Avenue, Cedar Grove, NJ 07009. (800) 233-0179 or (201) 857-2626 or (201) 256-2550.

  Summary: In this editorial, the authors call for an escalated research agenda for viral hepatitis. They stress that research efforts should be directed toward understanding the natural history of disease, defining the pathogenetic mechanisms of these viral infections, and developing effective preventive and therapeutic means to control the infections. They discuss the hepatitis B virus, the **hepatitis C virus,** other hepatotropic viruses, prevention with vaccination, and treatment options, including liver transplantation.

Academic Periodicals covering Hepatitis C Virus

Numerous periodicals are currently indexed within the National Library of Medicine's PubMed database that are known to publish articles relating to hepatitis C virus. In addition to these sources, you can search for articles covering hepatitis C virus that have been published by any of the periodicals listed in previous chapters. To find the latest studies published, go to **http://www.ncbi.nlm.nih.gov/pubmed**, type the name of the periodical into the search box, and click "Go."

If you want complete details about the historical contents of a journal, you can also visit the following Web site: **http://www.ncbi.nlm.nih.gov/entrez/jrbrowser.cgi**. Here, type in the name of the journal or its abbreviation, and you will receive an index of published articles. At **http://locatorplus.gov/**, you can retrieve more indexing information on medical periodicals (e.g. the name of the publisher). Select the button "Search LOCATORplus." Then type in the name of the journal and select the advanced search option "Journal Title Search."

CHAPTER 9. RESEARCHING MEDICATIONS

Overview

While a number of hard copy or CD-ROM resources are available for researching medications, a more flexible method is to use Internet-based databases. Broadly speaking, there are two sources of information on approved medications: public sources and private sources. We will emphasize free-to-use public sources.

U.S. Pharmacopeia

Because of historical investments by various organizations and the emergence of the Internet, it has become rather simple to learn about the medications recommended for hepatitis C virus. One such source is the United States Pharmacopeia. In 1820, eleven physicians met in Washington, D.C. to establish the first compendium of standard drugs for the United States. They called this compendium the U.S. Pharmacopeia (USP). Today, the USP is a non-profit organization consisting of 800 volunteer scientists, eleven elected officials, and 400 representatives of state associations and colleges of medicine and pharmacy. The USP is located in Rockville, Maryland, and its home page is located at **http://www.usp.org/**. The USP currently provides standards for over 3,700 medications. The resulting USP DI® Advice for the Patient® can be accessed through the National Library of Medicine of the National Institutes of Health. The database is partially derived from lists of federally approved medications in the Food and Drug Administration's (FDA) Drug Approvals database, located at **http://www.fda.gov/cder/da/da.htm**.

While the FDA database is rather large and difficult to navigate, the Phamacopeia is both user-friendly and free to use. It covers more than 9,000 prescription and over-the-counter medications. To access this database, simply type the following hyperlink into your Web browser: **http://www.nlm.nih.gov/medlineplus/druginformation.html**. To view examples of a given medication (brand names, category, description, preparation, proper use, precautions, side effects, etc.), simply follow the hyperlinks indicated within the United States Pharmacopeia (USP).

Below, we have compiled a list of medications associated with hepatitis C virus. If you would like more information on a particular medication, the provided hyperlinks will direct you to ample documentation (e.g. typical dosage, side effects, drug-interaction risks, etc.).

The following drugs have been mentioned in the Pharmacopeia and other sources as being potentially applicable to hepatitis C virus:

Antihemophilic Factor

- **Systemic - U.S. Brands:** Alphanate; Bioclate; Helixate; Helixate FS; Hemofil M; Humate-P; Hyate:C; Koate-HP; Kogenate; Kogenate FS; Monarc-M; Monoclate-P; Recombinate
  http://www.nlm.nih.gov/medlineplus/druginfo/uspdi/202671.html

Epoetin

- **Systemic - U.S. Brands:** Epogen; Procrit
  http://www.nlm.nih.gov/medlineplus/druginfo/uspdi/202214.html

Ribavirin

- **Systemic - U.S. Brands:** Copegus; Rebetol; Virazole
  http://www.nlm.nih.gov/medlineplus/druginfo/uspdi/202509.html

Ribavirin and Interferon ALFA-2B, Recombinant

- **Systemic - U.S. Brands:** Rebetron
  http://www.nlm.nih.gov/medlineplus/druginfo/uspdi/500032.html

Commercial Databases

In addition to the medications listed in the USP above, a number of commercial sites are available by subscription to physicians and their institutions. Or, you may be able to access these sources from your local medical library.

Mosby's Drug Consult™

Mosby's Drug Consult™ database (also available on CD-ROM and book format) covers 45,000 drug products including generics and international brands. It provides prescribing information, drug interactions, and patient information. Subscription information is available at the following hyperlink: **http://www.mosbysdrugconsult.com/**.

PDR*health*

The PDR*health* database is a free-to-use, drug information search engine that has been written for the public in layman's terms. It contains FDA-approved drug information adapted from the Physicians' Desk Reference (PDR) database. PDR*health* can be searched by brand name, generic name, or indication. It features multiple drug interactions reports. Search PDR*health* at **http://www.pdrhealth.com/drug_info/index.html**.

Other Web Sites

Drugs.com (**www.drugs.com**) reproduces the information in the Pharmacopeia as well as commercial information. You may also want to consider the Web site of the Medical Letter,

Inc. (**http://www.medletter.com/**) which allows users to download articles on various drugs and therapeutics for a nominal fee.

If you have any questions about a medical treatment, the FDA may have an office near you. Look for their number in the blue pages of the phone book. You can also contact the FDA through its toll-free number, 1-888-INFO-FDA (1-888-463-6332), or on the World Wide Web at **www.fda.gov**.

APPENDICES

APPENDIX A. PHYSICIAN RESOURCES

Overview

In this chapter, we focus on databases and Internet-based guidelines and information resources created or written for a professional audience.

NIH Guidelines

Commonly referred to as "clinical" or "professional" guidelines, the National Institutes of Health publish physician guidelines for the most common diseases. Publications are available at the following by relevant Institute[10]:

- Office of the Director (OD); guidelines consolidated across agencies available at **http://www.nih.gov/health/consumer/conkey.htm**
- National Institute of General Medical Sciences (NIGMS); fact sheets available at **http://www.nigms.nih.gov/news/facts/**
- National Library of Medicine (NLM); extensive encyclopedia (A.D.A.M., Inc.) with guidelines: **http://www.nlm.nih.gov/medlineplus/healthtopics.html**
- National Cancer Institute (NCI); guidelines available at **http://www.cancer.gov/cancerinfo/list.aspx?viewid=5f35036e-5497-4d86-8c2c-714a9f7c8d25**
- National Eye Institute (NEI); guidelines available at **http://www.nei.nih.gov/order/index.htm**
- National Heart, Lung, and Blood Institute (NHLBI); guidelines available at **http://www.nhlbi.nih.gov/guidelines/index.htm**
- National Human Genome Research Institute (NHGRI); research available at **http://www.genome.gov/page.cfm?pageID=10000375**
- National Institute on Aging (NIA); guidelines available at **http://www.nia.nih.gov/health/**

[10] These publications are typically written by one or more of the various NIH Institutes.

- National Institute on Alcohol Abuse and Alcoholism (NIAAA); guidelines available at **http://www.niaaa.nih.gov/publications/publications.htm**
- National Institute of Allergy and Infectious Diseases (NIAID); guidelines available at **http://www.niaid.nih.gov/publications/**
- National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS); fact sheets and guidelines available at **http://www.niams.nih.gov/hi/index.htm**
- National Institute of Child Health and Human Development (NICHD); guidelines available at **http://www.nichd.nih.gov/publications/pubskey.cfm**
- National Institute on Deafness and Other Communication Disorders (NIDCD); fact sheets and guidelines at **http://www.nidcd.nih.gov/health/**
- National Institute of Dental and Craniofacial Research (NIDCR); guidelines available at **http://www.nidr.nih.gov/health/**
- National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK); guidelines available at **http://www.niddk.nih.gov/health/health.htm**
- National Institute on Drug Abuse (NIDA); guidelines available at **http://www.nida.nih.gov/DrugAbuse.html**
- National Institute of Environmental Health Sciences (NIEHS); environmental health information available at **http://www.niehs.nih.gov/external/facts.htm**
- National Institute of Mental Health (NIMH); guidelines available at **http://www.nimh.nih.gov/practitioners/index.cfm**
- National Institute of Neurological Disorders and Stroke (NINDS); neurological disorder information pages available at **http://www.ninds.nih.gov/health_and_medical/disorder_index.htm**
- National Institute of Nursing Research (NINR); publications on selected illnesses at **http://www.nih.gov/ninr/news-info/publications.html**
- National Institute of Biomedical Imaging and Bioengineering; general information at **http://grants.nih.gov/grants/becon/becon_info.htm**
- Center for Information Technology (CIT); referrals to other agencies based on keyword searches available at **http://kb.nih.gov/www_query_main.asp**
- National Center for Complementary and Alternative Medicine (NCCAM); health information available at **http://nccam.nih.gov/health/**
- National Center for Research Resources (NCRR); various information directories available at **http://www.ncrr.nih.gov/publications.asp**
- Office of Rare Diseases; various fact sheets available at **http://rarediseases.info.nih.gov/html/resources/rep_pubs.html**
- Centers for Disease Control and Prevention; various fact sheets on infectious diseases available at **http://www.cdc.gov/publications.htm**

NIH Databases

In addition to the various Institutes of Health that publish professional guidelines, the NIH has designed a number of databases for professionals.[11] Physician-oriented resources provide a wide variety of information related to the biomedical and health sciences, both past and present. The format of these resources varies. Searchable databases, bibliographic citations, full-text articles (when available), archival collections, and images are all available. The following are referenced by the National Library of Medicine:[12]

- **Bioethics:** Access to published literature on the ethical, legal, and public policy issues surrounding healthcare and biomedical research. This information is provided in conjunction with the Kennedy Institute of Ethics located at Georgetown University, Washington, D.C.: **http://www.nlm.nih.gov/databases/databases_bioethics.html**
- **HIV/AIDS Resources:** Describes various links and databases dedicated to HIV/AIDS research: **http://www.nlm.nih.gov/pubs/factsheets/aidsinfs.html**
- **NLM Online Exhibitions:** Describes "Exhibitions in the History of Medicine": **http://www.nlm.nih.gov/exhibition/exhibition.html**. Additional resources for historical scholarship in medicine: **http://www.nlm.nih.gov/hmd/hmd.html**
- **Biotechnology Information:** Access to public databases. The National Center for Biotechnology Information conducts research in computational biology, develops software tools for analyzing genome data, and disseminates biomedical information for the better understanding of molecular processes affecting human health and disease: **http://www.ncbi.nlm.nih.gov/**
- **Population Information:** The National Library of Medicine provides access to worldwide coverage of population, family planning, and related health issues, including family planning technology and programs, fertility, and population law and policy: **http://www.nlm.nih.gov/databases/databases_population.html**
- **Cancer Information:** Access to cancer-oriented databases: **http://www.nlm.nih.gov/databases/databases_cancer.html**
- **Profiles in Science:** Offering the archival collections of prominent twentieth-century biomedical scientists to the public through modern digital technology: **http://www.profiles.nlm.nih.gov/**
- **Chemical Information:** Provides links to various chemical databases and references: **http://sis.nlm.nih.gov/Chem/ChemMain.html**
- **Clinical Alerts:** Reports the release of findings from the NIH-funded clinical trials where such release could significantly affect morbidity and mortality: **http://www.nlm.nih.gov/databases/alerts/clinical_alerts.html**
- **Space Life Sciences:** Provides links and information to space-based research (including NASA): **http://www.nlm.nih.gov/databases/databases_space.html**
- **MEDLINE:** Bibliographic database covering the fields of medicine, nursing, dentistry, veterinary medicine, the healthcare system, and the pre-clinical sciences: **http://www.nlm.nih.gov/databases/databases_medline.html**

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[11] Remember, for the general public, the National Library of Medicine recommends the databases referenced in MEDLINE*plus* (**http://medlineplus.gov/** or **http://www.nlm.nih.gov/medlineplus/databases.html**).

[12] See **http://www.nlm.nih.gov/databases/databases.html**.

- **Toxicology and Environmental Health Information (TOXNET):** Databases covering toxicology and environmental health: **http://sis.nlm.nih.gov/Tox/ToxMain.html**
- **Visible Human Interface:** Anatomically detailed, three-dimensional representations of normal male and female human bodies: **http://www.nlm.nih.gov/research/visible/visible_human.html**

The NLM Gateway[13]

The NLM (National Library of Medicine) Gateway is a Web-based system that lets users search simultaneously in multiple retrieval systems at the U.S. National Library of Medicine (NLM). It allows users of NLM services to initiate searches from one Web interface, providing one-stop searching for many of NLM's information resources or databases.[14] To use the NLM Gateway, simply go to the search site at **http://gateway.nlm.nih.gov/gw/Cmd**. Type "hepatitis C virus" (or synonyms) into the search box and click "Search." The results will be presented in a tabular form, indicating the number of references in each database category.

Results Summary

Category	Items Found
Journal Articles	18066
Books / Periodicals / Audio Visual	45
Consumer Health	907
Meeting Abstracts	935
Other Collections	55
Total	20008

HSTAT[15]

HSTAT is a free, Web-based resource that provides access to full-text documents used in healthcare decision-making.[16] These documents include clinical practice guidelines, quick-reference guides for clinicians, consumer health brochures, evidence reports and technology assessments from the Agency for Healthcare Research and Quality (AHRQ), as well as AHRQ's Put Prevention Into Practice.[17] Simply search by "hepatitis C virus" (or synonyms) at the following Web site: **http://text.nlm.nih.gov**.

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[13] Adapted from NLM: **http://gateway.nlm.nih.gov/gw/Cmd?Overview.x**.

[14] The NLM Gateway is currently being developed by the Lister Hill National Center for Biomedical Communications (LHNCBC) at the National Library of Medicine (NLM) of the National Institutes of Health (NIH).

[15] Adapted from HSTAT: **http://www.nlm.nih.gov/pubs/factsheets/hstat.html**.

[16] The HSTAT URL is **http://hstat.nlm.nih.gov/**.

[17] Other important documents in HSTAT include: the National Institutes of Health (NIH) Consensus Conference Reports and Technology Assessment Reports; the HIV/AIDS Treatment Information Service (ATIS) resource documents; the Substance Abuse and Mental Health Services Administration's Center for Substance Abuse Treatment (SAMHSA/CSAT) Treatment Improvement Protocols (TIP) and Center for Substance Abuse Prevention (SAMHSA/CSAP) Prevention Enhancement Protocols System (PEPS); the Public Health Service (PHS) Preventive Services Task Force's *Guide to Clinical Preventive Services*; the independent, nonfederal Task Force on Community Services' *Guide to Community Preventive Services*; and the Health Technology Advisory Committee (HTAC) of the Minnesota Health Care Commission (MHCC) health technology evaluations.

Coffee Break: Tutorials for Biologists[18]

Coffee Break is a general healthcare site that takes a scientific view of the news and covers recent breakthroughs in biology that may one day assist physicians in developing treatments. Here you will find a collection of short reports on recent biological discoveries. Each report incorporates interactive tutorials that demonstrate how bioinformatics tools are used as a part of the research process. Currently, all Coffee Breaks are written by NCBI staff.[19] Each report is about 400 words and is usually based on a discovery reported in one or more articles from recently published, peer-reviewed literature.[20] This site has new articles every few weeks, so it can be considered an online magazine of sorts. It is intended for general background information. You can access the Coffee Break Web site at the following hyperlink: **http://www.ncbi.nlm.nih.gov/Coffeebreak/**.

Other Commercial Databases

In addition to resources maintained by official agencies, other databases exist that are commercial ventures addressing medical professionals. Here are some examples that may interest you:

- **CliniWeb International:** Index and table of contents to selected clinical information on the Internet; see **http://www.ohsu.edu/cliniweb/**.
- **Medical World Search:** Searches full text from thousands of selected medical sites on the Internet; see **http://www.mwsearch.com/**.

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[18] Adapted from **http://www.ncbi.nlm.nih.gov/Coffeebreak/Archive/FAQ.html**.

[19] The figure that accompanies each article is frequently supplied by an expert external to NCBI, in which case the source of the figure is cited. The result is an interactive tutorial that tells a biological story.

[20] After a brief introduction that sets the work described into a broader context, the report focuses on how a molecular understanding can provide explanations of observed biology and lead to therapies for diseases. Each vignette is accompanied by a figure and hypertext links that lead to a series of pages that interactively show how NCBI tools and resources are used in the research process.

APPENDIX B. PATIENT RESOURCES

Overview

Official agencies, as well as federally funded institutions supported by national grants, frequently publish a variety of guidelines written with the patient in mind. These are typically called "Fact Sheets" or "Guidelines." They can take the form of a brochure, information kit, pamphlet, or flyer. Often they are only a few pages in length. Since new guidelines on hepatitis C virus can appear at any moment and be published by a number of sources, the best approach to finding guidelines is to systematically scan the Internet-based services that post them.

Patient Guideline Sources

The remainder of this chapter directs you to sources which either publish or can help you find additional guidelines on topics related to hepatitis C virus. Due to space limitations, these sources are listed in a concise manner. Do not hesitate to consult the following sources by either using the Internet hyperlink provided, or, in cases where the contact information is provided, contacting the publisher or author directly.

The National Institutes of Health

The NIH gateway to patients is located at **http://health.nih.gov/**. From this site, you can search across various sources and institutes, a number of which are summarized below.

Topic Pages: MEDLINEplus

The National Library of Medicine has created a vast and patient-oriented healthcare information portal called MEDLINEplus. Within this Internet-based system are "health topic pages" which list links to available materials relevant to hepatitis C virus. To access this system, log on to **http://www.nlm.nih.gov/medlineplus/healthtopics.html**. From there you can either search using the alphabetical index or browse by broad topic areas. Recently, MEDLINEplus listed the following when searched for "hepatitis C virus":

Hepatitis
http://www.nlm.nih.gov/medlineplus/hepatitis.html

Hepatitis A
http://www.nlm.nih.gov/medlineplus/hepatitisa.html

Hepatitis B
http://www.nlm.nih.gov/medlineplus/hepatitisb.html

Hepatitis C
http://www.nlm.nih.gov/medlineplus/hepatitisc.html

Liver Diseases
http://www.nlm.nih.gov/medlineplus/liverdiseases.html

You may also choose to use the search utility provided by MEDLINEplus at the following Web address: **http://www.nlm.nih.gov/medlineplus/**. Simply type a keyword into the search box and click "Search." This utility is similar to the NIH search utility, with the exception that it only includes materials that are linked within the MEDLINEplus system (mostly patient-oriented information). It also has the disadvantage of generating unstructured results. We recommend, therefore, that you use this method only if you have a very targeted search.

The Combined Health Information Database (CHID)

CHID Online is a reference tool that maintains a database directory of thousands of journal articles and patient education guidelines on hepatitis C virus. CHID offers summaries that describe the guidelines available, including contact information and pricing. CHID's general Web site is **http://chid.nih.gov/**. To search this database, go to **http://chid.nih.gov/detail/detail.html**. In particular, you can use the advanced search options to look up pamphlets, reports, brochures, and information kits. The following was recently posted in this archive:

- **Roles of Hepatitis C Virus Infection in Autoimmune Hepatitis**

  Source: in Tsuji, T., et al, eds. Molecular Biology and Immunology in Hepatology. St. Louis, MO: Elsevier Science. 2002. p. 219-227.

  Contact: Available from Elsevier Science. Customer Service Department, 11830 Westline Industrial Drive, St. Louis, MO 63146. (800) 545-2522. Fax (800) 535-9935. Email: usbkinfo@elsevier.com. Website: www.elsevierhealth.com. PRICE: $145.00. ISBN: 444506535.

  Summary: Autoimmune hepatitis (AIH) is a chronic, mainly periportal hepatitis associated with hypergammaglobulinemia and circulating antoantibodies, which in most cases responds to immunosuppressive treatment. This chapter on the role of **hepatitis C virus** (HCV) infection in AIH is from a text book on the pathogenesis and treatment of intractable liver diseases. Since the discovery of HCV, the most major causative agent of chronic hepatitis, issues regarding the pathogenesis and treatment of AIH have arisen. There is mounting evidence that HCV triggers and perhaps causes a multitude of autoimmune phenomena such as cryoglobulinemia, glomerulonephritis, Sjogren syndrome, and Hashimoto's disease. In this chapter, the author describes new developments regarding these issues, including findings from the author's laboratory. The author concludes that there are few lines of evidence showing that HCV infections

trigger the onset of AIH. However, various autoimmune phenomena are frequently observed in HCV infected patients. The specific therapeutic strategy should be established on a case-by-case basis, taking into consideration clinical features and laboratory data including HCV loads. 2 figures. 2 tables. 36 references.

- **Hepatitis C Prevention: Almost 4 Million Americans Have Been Infected With Hepatitis C Virus**

  Contact: CDC National Prevention Information Network, PO Box 6003, Rockville, MD, 20849-6003, (800) 458-5231, http://www.cdcnpin.org.

  Summary: This brochure for the general public discusses the prevention and transmission of hepatitis C and who is at risk of having the disease. Hepatitis C is a liver disease caused by the **hepatitis C virus** (HCV). The infection is spread by contact with blood infected by the virus. Some persons carry hepatitis C and do not feel sick from the disease. Others with liver damage due to HCV may develop cirrhosis (scarring) of the liver and liver failure. To aid in the prevention of hepatitis C, the brochure suggests not shooting drugs; using clean syringes, water, and drug works if persons do shoot drugs; not sharing toothbrushes, razors, or other items that may have blood on them; using routine barrier precautions and safely handling needles and sharps if persons are health care workers; and considering the health risks associated with tattooing and body piercing. HCV can be spread by sex, but this does not occur often. Persons having sex with more than one partner can get other diseases, should use latex condoms, should be vaccinated against hepatitis B, and may want to consider abstinence from sex. HCV is not spread by breast feeding, casual contact, food or water, sneezing, coughing, or sharing eating utensils or drinking glasses. Many people who are at risk for hepatitis C are at risk for hepatitis A and B. Persons should ask their doctors for a blood test for HCV if they have ever injected street drugs, were treated for clotting problems with a blood product made before 1987, received a blood transfusion or solid organ transplant before July 1992, were notified that they received blood that possibly contained HCV, or were ever on long-term kidney dialysis. Early diagnosis is important so persons can be checked for liver disease, get treatment if indicated, learn how to protect their livers from further harm, and learn how they can prevent spreading HCV to others.

- **Vaccinations for Adults With Hepatitis C Virus Infection**

  Contact: Immunization Action Coalition, 1573 Selby Ave Ste 234, St Paul, MN, 55104, (651) 647-9009, http://www.immunize.org.

  Summary: This fact sheet, written for individuals the **hepatitis C virus** (HCV), makes recommendations regarding vaccinations for persons with compromised immune systems. The fact sheet lists several diseases that can be prevented with periodic vaccinations. It provides a recommended schedule of shots for HCV-positive individuals, their caregivers, and roommates regarding the following diseases: pneumococcal, influenza, hepatitis A and B, tetanus/diptheria, measles, mumps, rubella, and varicella.

- **Frequently Asked Questions and Answers about Coinfection with HIV and Hepatitis C Virus**

  Contact: CDC National Prevention Information Network, PO Box 6003, Rockville, MD, 20849-6003, (800) 458-5231, http://www.cdcnpin.org.

  Summary: This information sheet discusses problems of coinfection with both the human immunodeficiency virus (HIV) and the **hepatitis C virus.** The sheet explains

which HIV positive individuals are most likely to be coinfected, the effects of coinfection on progression of both diseases, prevention suggestions, treatment options, and other disease management guidelines for persons living with HIV and hepatitis C. The information sheet also provides resources for further information.

- **Coinfection with HIV and Hepatitis C Virus**

  Contact: CDC National Prevention Information Network, PO Box 6003, Rockville, MD, 20849-6003, (800) 458-5231, http://www.cdcnpin.org.

  Summary: This pamphlet provides basic information about the **Hepatitis C virus** infection (HCV) for persons living with the human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS). It discusses the risk factors to HIV-infected persons for HCV infection, methods of transmission including the use of injection drugs and tattooing or body piercing, and treatment options for persons with HCV.

Healthfinder™

Healthfinder™ is sponsored by the U.S. Department of Health and Human Services and offers links to hundreds of other sites that contain healthcare information. This Web site is located at **http://www.healthfinder.gov**. Again, keyword searches can be used to find guidelines. The following was recently found in this database:

- **Hepatitis C: What Clinicians and Other Health Professionals Need to Know**

  Summary: A web-based training course on hepatitis C virus (HCV) infection designed for primary care physicians, infectious disease specialists, blood bank employees, public health professionals and other

  Source: Division of Viral Hepatitis, National Center for Infectious Diseases

  http://www.healthfinder.gov/scripts/recordpass.asp?RecordType=0&RecordID=5314

The NIH Search Utility

The NIH search utility allows you to search for documents on over 100 selected Web sites that comprise the NIH-WEB-SPACE. Each of these servers is "crawled" and indexed on an ongoing basis. Your search will produce a list of various documents, all of which will relate in some way to hepatitis C virus. The drawbacks of this approach are that the information is not organized by theme and that the references are often a mix of information for professionals and patients. Nevertheless, a large number of the listed Web sites provide useful background information. We can only recommend this route, therefore, for relatively rare or specific disorders, or when using highly targeted searches. To use the NIH search utility, visit the following Web page: **http://search.nih.gov/index.html**.

Additional Web Sources

A number of Web sites are available to the public that often link to government sites. These can also point you in the direction of essential information. The following is a representative sample:

- AOL: **http://search.aol.com/cat.adp?id=168&layer=&from=subcats**

- Family Village: **http://www.familyvillage.wisc.edu/specific.htm**
- Google: **http://directory.google.com/Top/Health/Conditions_and_Diseases/**
- Med Help International: **http://www.medhelp.org/HealthTopics/A.html**
- Open Directory Project: **http://dmoz.org/Health/Conditions_and_Diseases/**
- Yahoo.com: **http://dir.yahoo.com/Health/Diseases_and_Conditions/**
- WebMD®Health: **http://my.webmd.com/health_topics**

Finding Associations

There are several Internet directories that provide lists of medical associations with information on or resources relating to hepatitis C virus. By consulting all of associations listed in this chapter, you will have nearly exhausted all sources for patient associations concerned with hepatitis C virus.

The National Health Information Center (NHIC)

The National Health Information Center (NHIC) offers a free referral service to help people find organizations that provide information about hepatitis C virus. For more information, see the NHIC's Web site at **http://www.health.gov/NHIC/** or contact an information specialist by calling 1-800-336-4797.

Directory of Health Organizations

The Directory of Health Organizations, provided by the National Library of Medicine Specialized Information Services, is a comprehensive source of information on associations. The Directory of Health Organizations database can be accessed via the Internet at **http://www.sis.nlm.nih.gov/Dir/DirMain.html**. It is composed of two parts: DIRLINE and Health Hotlines.

The DIRLINE database comprises some 10,000 records of organizations, research centers, and government institutes and associations that primarily focus on health and biomedicine. To access DIRLINE directly, go to the following Web site: **http://dirline.nlm.nih.gov/**. Simply type in "hepatitis C virus" (or a synonym), and you will receive information on all relevant organizations listed in the database.

Health Hotlines directs you to toll-free numbers to over 300 organizations. You can access this database directly at **http://www.sis.nlm.nih.gov/hotlines/**. On this page, you are given the option to search by keyword or by browsing the subject list. When you have received your search results, click on the name of the organization for its description and contact information.

The Combined Health Information Database

Another comprehensive source of information on healthcare associations is the Combined Health Information Database. Using the "Detailed Search" option, you will need to limit

your search to "Organizations" and "hepatitis C virus". Type the following hyperlink into your Web browser: **http://chid.nih.gov/detail/detail.html**. To find associations, use the drop boxes at the bottom of the search page where "You may refine your search by." For publication date, select "All Years." Then, select your preferred language and the format option "Organization Resource Sheet." Type "hepatitis C virus" (or synonyms) into the "For these words:" box. You should check back periodically with this database since it is updated every three months.

The National Organization for Rare Disorders, Inc.

The National Organization for Rare Disorders, Inc. has prepared a Web site that provides, at no charge, lists of associations organized by health topic. You can access this database at the following Web site: **http://www.rarediseases.org/search/orgsearch.html**. Type "hepatitis C virus" (or a synonym) into the search box, and click "Submit Query."

APPENDIX C. FINDING MEDICAL LIBRARIES

Overview

In this Appendix, we show you how to quickly find a medical library in your area.

Preparation

Your local public library and medical libraries have interlibrary loan programs with the National Library of Medicine (NLM), one of the largest medical collections in the world. According to the NLM, most of the literature in the general and historical collections of the National Library of Medicine is available on interlibrary loan to any library. If you would like to access NLM medical literature, then visit a library in your area that can request the publications for you.[21]

Finding a Local Medical Library

The quickest method to locate medical libraries is to use the Internet-based directory published by the National Network of Libraries of Medicine (NN/LM). This network includes 4626 members and affiliates that provide many services to librarians, health professionals, and the public. To find a library in your area, simply visit **http://nnlm.gov/members/adv.html** or call 1-800-338-7657.

Medical Libraries in the U.S. and Canada

In addition to the NN/LM, the National Library of Medicine (NLM) lists a number of libraries with reference facilities that are open to the public. The following is the NLM's list and includes hyperlinks to each library's Web site. These Web pages can provide information on hours of operation and other restrictions. The list below is a small sample of

[21] Adapted from the NLM: **http://www.nlm.nih.gov/psd/cas/interlibrary.html**.

libraries recommended by the National Library of Medicine (sorted alphabetically by name of the U.S. state or Canadian province where the library is located)[22]:

- **Alabama:** Health InfoNet of Jefferson County (Jefferson County Library Cooperative, Lister Hill Library of the Health Sciences), **http://www.uab.edu/infonet/**
- **Alabama:** Richard M. Scrushy Library (American Sports Medicine Institute)
- **Arizona:** Samaritan Regional Medical Center: The Learning Center (Samaritan Health System, Phoenix, Arizona), **http://www.samaritan.edu/library/bannerlibs.htm**
- **California:** Kris Kelly Health Information Center (St. Joseph Health System, Humboldt), **http://www.humboldt1.com/~kkhic/index.html**
- **California:** Community Health Library of Los Gatos, **http://www.healthlib.org/orgresources.html**
- **California:** Consumer Health Program and Services (CHIPS) (County of Los Angeles Public Library, Los Angeles County Harbor-UCLA Medical Center Library) - Carson, CA, **http://www.colapublib.org/services/chips.html**
- **California:** Gateway Health Library (Sutter Gould Medical Foundation)
- **California:** Health Library (Stanford University Medical Center), **http://www-med.stanford.edu/healthlibrary/**
- **California:** Patient Education Resource Center - Health Information and Resources (University of California, San Francisco), **http://sfghdean.ucsf.edu/barnett/PERC/default.asp**
- **California:** Redwood Health Library (Petaluma Health Care District), **http://www.phcd.org/rdwdlib.html**
- **California:** Los Gatos PlaneTree Health Library, **http://planetreesanjose.org/**
- **California:** Sutter Resource Library (Sutter Hospitals Foundation, Sacramento), **http://suttermedicalcenter.org/library/**
- **California:** Health Sciences Libraries (University of California, Davis), **http://www.lib.ucdavis.edu/healthsci/**
- **California:** ValleyCare Health Library & Ryan Comer Cancer Resource Center (ValleyCare Health System, Pleasanton), **http://gaelnet.stmarys-ca.edu/other.libs/gbal/east/vchl.html**
- **California:** Washington Community Health Resource Library (Fremont), **http://www.healthlibrary.org/**
- **Colorado:** William V. Gervasini Memorial Library (Exempla Healthcare), **http://www.saintjosephdenver.org/yourhealth/libraries/**
- **Connecticut:** Hartford Hospital Health Science Libraries (Hartford Hospital), **http://www.harthosp.org/library/**
- **Connecticut:** Healthnet: Connecticut Consumer Health Information Center (University of Connecticut Health Center, Lyman Maynard Stowe Library), **http://library.uchc.edu/departm/hnet/**

[22] Abstracted from **http://www.nlm.nih.gov/medlineplus/libraries.html**.

- **Connecticut:** Waterbury Hospital Health Center Library (Waterbury Hospital, Waterbury), **http://www.waterburyhospital.com/library/consumer.shtml**
- **Delaware:** Consumer Health Library (Christiana Care Health System, Eugene du Pont Preventive Medicine & Rehabilitation Institute, Wilmington), **http://www.christianacare.org/health_guide/health_guide_pmri_health_info.cfm**
- **Delaware:** Lewis B. Flinn Library (Delaware Academy of Medicine, Wilmington), **http://www.delamed.org/chls.html**
- **Georgia:** Family Resource Library (Medical College of Georgia, Augusta), **http://cmc.mcg.edu/kids_families/fam_resources/fam_res_lib/frl.htm**
- **Georgia:** Health Resource Center (Medical Center of Central Georgia, Macon), **http://www.mccg.org/hrc/hrchome.asp**
- **Hawaii:** Hawaii Medical Library: Consumer Health Information Service (Hawaii Medical Library, Honolulu), **http://hml.org/CHIS/**
- **Idaho:** DeArmond Consumer Health Library (Kootenai Medical Center, Coeur d'Alene), **http://www.nicon.org/DeArmond/index.htm**
- **Illinois:** Health Learning Center of Northwestern Memorial Hospital (Chicago), **http://www.nmh.org/health_info/hlc.html**
- **Illinois:** Medical Library (OSF Saint Francis Medical Center, Peoria), **http://www.osfsaintfrancis.org/general/library/**
- **Kentucky:** Medical Library - Services for Patients, Families, Students & the Public (Central Baptist Hospital, Lexington), **http://www.centralbap.com/education/community/library.cfm**
- **Kentucky:** University of Kentucky - Health Information Library (Chandler Medical Center, Lexington), **http://www.mc.uky.edu/PatientEd/**
- **Louisiana:** Alton Ochsner Medical Foundation Library (Alton Ochsner Medical Foundation, New Orleans), **http://www.ochsner.org/library/**
- **Louisiana:** Louisiana State University Health Sciences Center Medical Library-Shreveport, **http://lib-sh.lsuhsc.edu/**
- **Maine:** Franklin Memorial Hospital Medical Library (Franklin Memorial Hospital, Farmington), **http://www.fchn.org/fmh/lib.htm**
- **Maine:** Gerrish-True Health Sciences Library (Central Maine Medical Center, Lewiston), **http://www.cmmc.org/library/library.html**
- **Maine:** Hadley Parrot Health Science Library (Eastern Maine Healthcare, Bangor), **http://www.emh.org/hll/hpl/guide.htm**
- **Maine:** Maine Medical Center Library (Maine Medical Center, Portland), **http://www.mmc.org/library/**
- **Maine:** Parkview Hospital (Brunswick), **http://www.parkviewhospital.org/**
- **Maine:** Southern Maine Medical Center Health Sciences Library (Southern Maine Medical Center, Biddeford), **http://www.smmc.org/services/service.php3?choice=10**
- **Maine:** Stephens Memorial Hospital's Health Information Library (Western Maine Health, Norway), **http://www.wmhcc.org/Library/**

- **Manitoba, Canada:** Consumer & Patient Health Information Service (University of Manitoba Libraries), **http://www.umanitoba.ca/libraries/units/health/reference/chis.html**
- **Manitoba, Canada:** J.W. Crane Memorial Library (Deer Lodge Centre, Winnipeg), **http://www.deerlodge.mb.ca/crane_library/about.asp**
- **Maryland:** Health Information Center at the Wheaton Regional Library (Montgomery County, Dept. of Public Libraries, Wheaton Regional Library), **http://www.mont.lib.md.us/healthinfo/hic.asp**
- **Massachusetts:** Baystate Medical Center Library (Baystate Health System), **http://www.baystatehealth.com/1024/**
- **Massachusetts:** Boston University Medical Center Alumni Medical Library (Boston University Medical Center), **http://med-libwww.bu.edu/library/lib.html**
- **Massachusetts:** Lowell General Hospital Health Sciences Library (Lowell General Hospital, Lowell), **http://www.lowellgeneral.org/library/HomePageLinks/WWW.htm**
- **Massachusetts:** Paul E. Woodard Health Sciences Library (New England Baptist Hospital, Boston), **http://www.nebh.org/health_lib.asp**
- **Massachusetts:** St. Luke's Hospital Health Sciences Library (St. Luke's Hospital, Southcoast Health System, New Bedford), **http://www.southcoast.org/library/**
- **Massachusetts:** Treadwell Library Consumer Health Reference Center (Massachusetts General Hospital), **http://www.mgh.harvard.edu/library/chrcindex.html**
- **Massachusetts:** UMass HealthNet (University of Massachusetts Medical School, Worchester), **http://healthnet.umassmed.edu/**
- **Michigan:** Botsford General Hospital Library - Consumer Health (Botsford General Hospital, Library & Internet Services), **http://www.botsfordlibrary.org/consumer.htm**
- **Michigan:** Helen DeRoy Medical Library (Providence Hospital and Medical Centers), **http://www.providence-hospital.org/library/**
- **Michigan:** Marquette General Hospital - Consumer Health Library (Marquette General Hospital, Health Information Center), **http://www.mgh.org/center.html**
- **Michigan:** Patient Education Resouce Center - University of Michigan Cancer Center (University of Michigan Comprehensive Cancer Center, Ann Arbor), **http://www.cancer.med.umich.edu/learn/leares.htm**
- **Michigan:** Sladen Library & Center for Health Information Resources - Consumer Health Information (Detroit), **http://www.henryford.com/body.cfm?id=39330**
- **Montana:** Center for Health Information (St. Patrick Hospital and Health Sciences Center, Missoula)
- **National:** Consumer Health Library Directory (Medical Library Association, Consumer and Patient Health Information Section), **http://caphis.mlanet.org/directory/index.html**
- **National:** National Network of Libraries of Medicine (National Library of Medicine) - provides library services for health professionals in the United States who do not have access to a medical library, **http://nnlm.gov/**
- **National:** NN/LM List of Libraries Serving the Public (National Network of Libraries of Medicine), **http://nnlm.gov/members/**

- **Nevada:** Health Science Library, West Charleston Library (Las Vegas-Clark County Library District, Las Vegas), **http://www.lvccld.org/special_collections/medical/index.htm**
- **New Hampshire:** Dartmouth Biomedical Libraries (Dartmouth College Library, Hanover), **http://www.dartmouth.edu/~biomed/resources.htmld/conshealth.htmld/**
- **New Jersey:** Consumer Health Library (Rahway Hospital, Rahway), **http://www.rahwayhospital.com/library.htm**
- **New Jersey:** Dr. Walter Phillips Health Sciences Library (Englewood Hospital and Medical Center, Englewood), **http://www.englewoodhospital.com/links/index.htm**
- **New Jersey:** Meland Foundation (Englewood Hospital and Medical Center, Englewood), **http://www.geocities.com/ResearchTriangle/9360/**
- **New York:** Choices in Health Information (New York Public Library) - NLM Consumer Pilot Project participant, **http://www.nypl.org/branch/health/links.html**
- **New York:** Health Information Center (Upstate Medical University, State University of New York, Syracuse), **http://www.upstate.edu/library/hic/**
- **New York:** Health Sciences Library (Long Island Jewish Medical Center, New Hyde Park), **http://www.lij.edu/library/library.html**
- **New York:** ViaHealth Medical Library (Rochester General Hospital), **http://www.nyam.org/library/**
- **Ohio:** Consumer Health Library (Akron General Medical Center, Medical & Consumer Health Library), **http://www.akrongeneral.org/hwlibrary.htm**
- **Oklahoma:** The Health Information Center at Saint Francis Hospital (Saint Francis Health System, Tulsa), **http://www.sfh-tulsa.com/services/healthinfo.asp**
- **Oregon:** Planetree Health Resource Center (Mid-Columbia Medical Center, The Dalles), **http://www.mcmc.net/phrc/**
- **Pennsylvania:** Community Health Information Library (Milton S. Hershey Medical Center, Hershey), **http://www.hmc.psu.edu/commhealth/**
- **Pennsylvania:** Community Health Resource Library (Geisinger Medical Center, Danville), **http://www.geisinger.edu/education/commlib.shtml**
- **Pennsylvania:** HealthInfo Library (Moses Taylor Hospital, Scranton), **http://www.mth.org/healthwellness.html**
- **Pennsylvania:** Hopwood Library (University of Pittsburgh, Health Sciences Library System, Pittsburgh), **http://www.hsls.pitt.edu/guides/chi/hopwood/index_html**
- **Pennsylvania:** Koop Community Health Information Center (College of Physicians of Philadelphia), **http://www.collphyphil.org/kooppg1.shtml**
- **Pennsylvania:** Learning Resources Center - Medical Library (Susquehanna Health System, Williamsport), **http://www.shscares.org/services/lrc/index.asp**
- **Pennsylvania:** Medical Library (UPMC Health System, Pittsburgh), **http://www.upmc.edu/passavant/library.htm**
- **Quebec, Canada:** Medical Library (Montreal General Hospital), **http://www.mghlib.mcgill.ca/**

- **South Dakota:** Rapid City Regional Hospital Medical Library (Rapid City Regional Hospital), **http://www.rcrh.org/Services/Library/Default.asp**
- **Texas:** Houston HealthWays (Houston Academy of Medicine-Texas Medical Center Library), **http://hhw.library.tmc.edu/**
- **Washington:** Community Health Library (Kittitas Valley Community Hospital), **http://www.kvch.com/**
- **Washington:** Southwest Washington Medical Center Library (Southwest Washington Medical Center, Vancouver), **http://www.swmedicalcenter.com/body.cfm?id=72**

ONLINE GLOSSARIES

The Internet provides access to a number of free-to-use medical dictionaries. The National Library of Medicine has compiled the following list of online dictionaries:

- ADAM Medical Encyclopedia (A.D.A.M., Inc.), comprehensive medical reference: **http://www.nlm.nih.gov/medlineplus/encyclopedia.html**
- MedicineNet.com Medical Dictionary (MedicineNet, Inc.): **http://www.medterms.com/Script/Main/hp.asp**
- Merriam-Webster Medical Dictionary (Inteli-Health, Inc.): **http://www.intelihealth.com/IH/**
- Multilingual Glossary of Technical and Popular Medical Terms in Eight European Languages (European Commission) - Danish, Dutch, English, French, German, Italian, Portuguese, and Spanish: **http://allserv.rug.ac.be/~rvdstich/eugloss/welcome.html**
- On-line Medical Dictionary (CancerWEB): **http://cancerweb.ncl.ac.uk/omd/**
- Rare Diseases Terms (Office of Rare Diseases): **http://ord.aspensys.com/asp/diseases/diseases.asp**
- Technology Glossary (National Library of Medicine) - Health Care Technology: **http://www.nlm.nih.gov/nichsr/ta101/ta10108.htm**

Beyond these, MEDLINEplus contains a very patient-friendly encyclopedia covering every aspect of medicine (licensed from A.D.A.M., Inc.). The ADAM Medical Encyclopedia can be accessed at **http://www.nlm.nih.gov/medlineplus/encyclopedia.html**. ADAM is also available on commercial Web sites such as drkoop.com (**http://www.drkoop.com/**) and Web MD (**http://my.webmd.com/adam/asset/adam_disease_articles/a_to_z/a**).

Online Dictionary Directories

The following are additional online directories compiled by the National Library of Medicine, including a number of specialized medical dictionaries:

- Medical Dictionaries: Medical & Biological (World Health Organization): **http://www.who.int/hlt/virtuallibrary/English/diction.htm#Medical**
- MEL-Michigan Electronic Library List of Online Health and Medical Dictionaries (Michigan Electronic Library): **http://mel.lib.mi.us/health/health-dictionaries.html**
- Patient Education: Glossaries (DMOZ Open Directory Project): **http://dmoz.org/Health/Education/Patient_Education/Glossaries/**
- Web of Online Dictionaries (Bucknell University): **http://www.yourdictionary.com/diction5.html#medicine**

HEPATITIS C VIRUS DICTIONARY

The definitions below are derived from official public sources, including the National Institutes of Health [NIH] and the European Union [EU].

Abdominal: Having to do with the abdomen, which is the part of the body between the chest and the hips that contains the pancreas, stomach, intestines, liver, gallbladder, and other organs. [NIH]

Abortion: 1. The premature expulsion from the uterus of the products of conception - of the embryo, or of a nonviable fetus. The four classic symptoms, usually present in each type of abortion, are uterine contractions, uterine haemorrhage, softening and dilatation of the cervix, and presentation or expulsion of all or part of the products of conception. 2. Premature stoppage of a natural or a pathological process. [EU]

Abscess: A localized, circumscribed collection of pus. [NIH]

Acceptor: A substance which, while normally not oxidized by oxygen or reduced by hydrogen, can be oxidized or reduced in presence of a substance which is itself undergoing oxidation or reduction. [NIH]

Acetaminophen: Analgesic antipyretic derivative of acetanilide. It has weak anti-inflammatory properties and is used as a common analgesic, but may cause liver, blood cell, and kidney damage. [NIH]

Acetylgalactosamine: The N-acetyl derivative of galactosamine. [NIH]

Acetylglucosamine: The N-acetyl derivative of glucosamine. [NIH]

Acquired Immunodeficiency Syndrome: An acquired defect of cellular immunity associated with infection by the human immunodeficiency virus (HIV), a CD4-positive T-lymphocyte count under 200 cells/microliter or less than 14% of total lymphocytes, and increased susceptibility to opportunistic infections and malignant neoplasms. Clinical manifestations also include emaciation (wasting) and dementia. These elements reflect criteria for AIDS as defined by the CDC in 1993. [NIH]

Actin: Essential component of the cell skeleton. [NIH]

Actinin: A protein factor that regulates the length of R-actin. It is chemically similar, but immunochemically distinguishable from actin. [NIH]

Acute Disease: Disease having a short and relatively severe course. [NIH]

Acute myelogenous leukemia: AML. A quickly progressing disease in which too many immature blood-forming cells are found in the blood and bone marrow. Also called acute myeloid leukemia or acute nonlymphocytic leukemia. [NIH]

Acute myeloid leukemia: AML. A quickly progressing disease in which too many immature blood-forming cells are found in the blood and bone marrow. Also called acute myelogenous leukemia or acute nonlymphocytic leukemia. [NIH]

Acute nonlymphocytic leukemia: A quickly progressing disease in which too many immature blood-forming cells are found in the blood and bone marrow. Also called acute myeloid leukemia or acute myelogenous leukemia. [NIH]

Adaptation: 1. The adjustment of an organism to its environment, or the process by which it enhances such fitness. 2. The normal ability of the eye to adjust itself to variations in the intensity of light; the adjustment to such variations. 3. The decline in the frequency of firing of a neuron, particularly of a receptor, under conditions of constant stimulation. 4. In

dentistry, (a) the proper fitting of a denture, (b) the degree of proximity and interlocking of restorative material to a tooth preparation, (c) the exact adjustment of bands to teeth. 5. In microbiology, the adjustment of bacterial physiology to a new environment. [EU]

Adduct: Complex formed when a carcinogen combines with DNA or a protein. [NIH]

Adenocarcinoma: A malignant epithelial tumor with a glandular organization. [NIH]

Adenoma: A benign epithelial tumor with a glandular organization. [NIH]

Adjunctive Therapy: Another treatment used together with the primary treatment. Its purpose is to assist the primary treatment. [NIH]

Adjustment: The dynamic process wherein the thoughts, feelings, behavior, and biophysiological mechanisms of the individual continually change to adjust to the environment. [NIH]

Adsorption: The condensation of gases, liquids, or dissolved substances on the surfaces of solids. It includes adsorptive phenomena of bacteria and viruses as well as of tissues treated with exogenous drugs and chemicals. [NIH]

Adsorptive: It captures volatile compounds by binding them to agents such as activated carbon or adsorptive resins. [NIH]

Adverse Effect: An unwanted side effect of treatment. [NIH]

Aerobic: In biochemistry, reactions that need oxygen to happen or happen when oxygen is present. [NIH]

Affinity: 1. Inherent likeness or relationship. 2. A special attraction for a specific element, organ, or structure. 3. Chemical affinity; the force that binds atoms in molecules; the tendency of substances to combine by chemical reaction. 4. The strength of noncovalent chemical binding between two substances as measured by the dissociation constant of the complex. 5. In immunology, a thermodynamic expression of the strength of interaction between a single antigen-binding site and a single antigenic determinant (and thus of the stereochemical compatibility between them), most accurately applied to interactions among simple, uniform antigenic determinants such as haptens. Expressed as the association constant (K litres mole -1), which, owing to the heterogeneity of affinities in a population of antibody molecules of a given specificity, actually represents an average value (mean intrinsic association constant). 6. The reciprocal of the dissociation constant. [EU]

Age of Onset: The age or period of life at which a disease or the initial symptoms or manifestations of a disease appear in an individual. [NIH]

Alanine: A non-essential amino acid that occurs in high levels in its free state in plasma. It is produced from pyruvate by transamination. It is involved in sugar and acid metabolism, increases immunity, and provides energy for muscle tissue, brain, and the central nervous system. [NIH]

Algorithms: A procedure consisting of a sequence of algebraic formulas and/or logical steps to calculate or determine a given task. [NIH]

Alimentary: Pertaining to food or nutritive material, or to the organs of digestion. [EU]

Alkaline: Having the reactions of an alkali. [EU]

Alkaline Phosphatase: An enzyme that catalyzes the conversion of an orthophosphoric monoester and water to an alcohol and orthophosphate. EC 3.1.3.1. [NIH]

Alkaloid: A member of a large group of chemicals that are made by plants and have nitrogen in them. Some alkaloids have been shown to work against cancer. [NIH]

Alleles: Mutually exclusive forms of the same gene, occupying the same locus on homologous chromosomes, and governing the same biochemical and developmental

process. [NIH]

Allograft: An organ or tissue transplant between two humans. [NIH]

Alternative medicine: Practices not generally recognized by the medical community as standard or conventional medical approaches and used instead of standard treatments. Alternative medicine includes the taking of dietary supplements, megadose vitamins, and herbal preparations; the drinking of special teas; and practices such as massage therapy, magnet therapy, spiritual healing, and meditation. [NIH]

Amantadine: An antiviral that is used in the prophylactic or symptomatic treatment of Influenza A. It is also used as an antiparkinsonian agent, to treat extrapyramidal reactions, and for postherpetic neuralgia. The mechanisms of its effects in movement disorders are not well understood but probably reflect an increase in synthesis and release of dopamine, with perhaps some inhibition of dopamine uptake. [NIH]

Amino acid: Any organic compound containing an amino (-NH2 and a carboxyl (- COOH) group. The 20 a-amino acids listed in the accompanying table are the amino acids from which proteins are synthesized by formation of peptide bonds during ribosomal translation of messenger RNA; all except glycine, which is not optically active, have the L configuration. Other amino acids occurring in proteins, such as hydroxyproline in collagen, are formed by posttranslational enzymatic modification of amino acids residues in polypeptide chains. There are also several important amino acids, such as the neurotransmitter y-aminobutyric acid, that have no relation to proteins. Abbreviated AA. [EU]

Amino Acid Motifs: Commonly observed structural components of proteins formed by simple combinations of adjacent secondary structures. A commonly observed structure may be composed of a conserved sequence which can be represented by a consensus sequence. [NIH]

Amino Acid Sequence: The order of amino acids as they occur in a polypeptide chain. This is referred to as the primary structure of proteins. It is of fundamental importance in determining protein conformation. [NIH]

Amino Acid Substitution: The naturally occurring or experimentally induced replacement of one or more amino acids in a protein with another. If a functionally equivalent amino acid is substituted, the protein may retain wild-type activity. Substitution may also diminish or eliminate protein function. Experimentally induced substitution is often used to study enzyme activities and binding site properties. [NIH]

Aminoethyl: A protease inhibitor. [NIH]

Amphetamines: Analogs or derivatives of amphetamine. Many are sympathomimetics and central nervous system stimulators causing excitation, vasopression, bronchodilation, and to varying degrees, anorexia, analepsis, nasal decongestion, and some smooth muscle relaxation. [NIH]

Amplification: The production of additional copies of a chromosomal DNA sequence, found as either intrachromosomal or extrachromosomal DNA. [NIH]

Ampulla: A sac-like enlargement of a canal or duct. [NIH]

Anaesthesia: Loss of feeling or sensation. Although the term is used for loss of tactile sensibility, or of any of the other senses, it is applied especially to loss of the sensation of pain, as it is induced to permit performance of surgery or other painful procedures. [EU]

Anal: Having to do with the anus, which is the posterior opening of the large bowel. [NIH]

Analgesic: An agent that alleviates pain without causing loss of consciousness. [EU]

Analog: In chemistry, a substance that is similar, but not identical, to another. [NIH]

Analogous: Resembling or similar in some respects, as in function or appearance, but not in

origin or development;. [EU]

Anaphylatoxins: The family of peptides C3a, C4a, C5a, and C5a des-arginine produced in the serum during complement activation. They produce smooth muscle contraction, mast cell histamine release, affect platelet aggregation, and act as mediators of the local inflammatory process. The order of anaphylatoxin activity from strongest to weakest is C5a, C3a, C4a, and C5a des-arginine. The latter is the so-called "classical" anaphylatoxin but shows no spasmogenic activity though it contains some chemotactic ability. [NIH]

Anatomical: Pertaining to anatomy, or to the structure of the organism. [EU]

Anemia: A reduction in the number of circulating erythrocytes or in the quantity of hemoglobin. [NIH]

Angiogenesis: Blood vessel formation. Tumor angiogenesis is the growth of blood vessels from surrounding tissue to a solid tumor. This is caused by the release of chemicals by the tumor. [NIH]

Animal model: An animal with a disease either the same as or like a disease in humans. Animal models are used to study the development and progression of diseases and to test new treatments before they are given to humans. Animals with transplanted human cancers or other tissues are called xenograft models. [NIH]

Anionic: Pertaining to or containing an anion. [EU]

Anions: Negatively charged atoms, radicals or groups of atoms which travel to the anode or positive pole during electrolysis. [NIH]

Annealing: The spontaneous alignment of two single DNA strands to form a double helix. [NIH]

Antibacterial: A substance that destroys bacteria or suppresses their growth or reproduction. [EU]

Antibiotic: A drug used to treat infections caused by bacteria and other microorganisms. [NIH]

Antibodies: Immunoglobulin molecules having a specific amino acid sequence by virtue of which they interact only with the antigen that induced their synthesis in cells of the lymphoid series (especially plasma cells), or with an antigen closely related to it. [NIH]

Antibodies, Anticardiolipin: Antiphospholipid antibodies found in association with systemic lupus erythematosus (lupus erythematosus, systemic), antiphospholipid syndrome, and in a variety of other diseases as well as in healthy individuals. The antibodies are detected by solid-phase immunoassay employing the purified phospholipid antigen cardiolipin. [NIH]

Antibody: A type of protein made by certain white blood cells in response to a foreign substance (antigen). Each antibody can bind to only a specific antigen. The purpose of this binding is to help destroy the antigen. Antibodies can work in several ways, depending on the nature of the antigen. Some antibodies destroy antigens directly. Others make it easier for white blood cells to destroy the antigen. [NIH]

Anticoagulant: A drug that helps prevent blood clots from forming. Also called a blood thinner. [NIH]

Antigen: Any substance which is capable, under appropriate conditions, of inducing a specific immune response and of reacting with the products of that response, that is, with specific antibody or specifically sensitized T-lymphocytes, or both. Antigens may be soluble substances, such as toxins and foreign proteins, or particulate, such as bacteria and tissue cells; however, only the portion of the protein or polysaccharide molecule known as the antigenic determinant (q.v.) combines with antibody or a specific receptor on a lymphocyte.

Abbreviated Ag. [EU]

Antigen-Antibody Complex: The complex formed by the binding of antigen and antibody molecules. The deposition of large antigen-antibody complexes leading to tissue damage causes immune complex diseases. [NIH]

Antigen-presenting cell: APC. A cell that shows antigen on its surface to other cells of the immune system. This is an important part of an immune response. [NIH]

Anti-inflammatory: Having to do with reducing inflammation. [NIH]

Antimetabolite: A chemical that is very similar to one required in a normal biochemical reaction in cells. Antimetabolites can stop or slow down the reaction. [NIH]

Antimicrobial: Killing microorganisms, or suppressing their multiplication or growth. [EU]

Antineoplastic: Inhibiting or preventing the development of neoplasms, checking the maturation and proliferation of malignant cells. [EU]

Antioxidant: A substance that prevents damage caused by free radicals. Free radicals are highly reactive chemicals that often contain oxygen. They are produced when molecules are split to give products that have unpaired electrons. This process is called oxidation. [NIH]

Antiphospholipid Syndrome: The presence of antibodies directed against phospholipids (antibodies, antiphospholipid). The condition is associated with a variety of diseases, notably systemic lupus erythematosus and other connective tissue diseases, thrombopenia, and arterial or venous thromboses. In pregnancy it can cause abortion. Of the phospholipids, the cardiolipins show markedly elevated levels of anticardiolipin antibodies (antibodies, anticardiolipin). Present also are high levels of lupus anticoagulant (lupus coagulation inhibitor). [NIH]

Antiproliferative: Counteracting a process of proliferation. [EU]

Antiviral: Destroying viruses or suppressing their replication. [EU]

Antiviral Agents: Agents used in the prophylaxis or therapy of virus diseases. Some of the ways they may act include preventing viral replication by inhibiting viral DNA polymerase; binding to specific cell-surface receptors and inhibiting viral penetration or uncoating; inhibiting viral protein synthesis; or blocking late stages of virus assembly. [NIH]

Anus: The opening of the rectum to the outside of the body. [NIH]

Apheresis: Components being separated out, as leukapheresis, plasmapheresis, plateletpheresis. [NIH]

Apolipoproteins: The protein components of lipoproteins which remain after the lipids to which the proteins are bound have been removed. They play an important role in lipid transport and metabolism. [NIH]

Apoptosis: One of the two mechanisms by which cell death occurs (the other being the pathological process of necrosis). Apoptosis is the mechanism responsible for the physiological deletion of cells and appears to be intrinsically programmed. It is characterized by distinctive morphologic changes in the nucleus and cytoplasm, chromatin cleavage at regularly spaced sites, and the endonucleolytic cleavage of genomic DNA (DNA fragmentation) at internucleosomal sites. This mode of cell death serves as a balance to mitosis in regulating the size of animal tissues and in mediating pathologic processes associated with tumor growth. [NIH]

Approximate: Approximal [EU]

Arginine: An essential amino acid that is physiologically active in the L-form. [NIH]

Arterial: Pertaining to an artery or to the arteries. [EU]

Arteries: The vessels carrying blood away from the heart. [NIH]

Arterioles: The smallest divisions of the arteries located between the muscular arteries and the capillaries. [NIH]

Artery: Vessel-carrying blood from the heart to various parts of the body. [NIH]

Ascites: Accumulation or retention of free fluid within the peritoneal cavity. [NIH]

Aspartate: A synthetic amino acid. [NIH]

Assay: Determination of the amount of a particular constituent of a mixture, or of the biological or pharmacological potency of a drug. [EU]

Asymptomatic: Having no signs or symptoms of disease. [NIH]

Attenuated: Strain with weakened or reduced virulence. [NIH]

Attenuation: Reduction of transmitted sound energy or its electrical equivalent. [NIH]

Autoantibodies: Antibodies that react with self-antigens (autoantigens) of the organism that produced them. [NIH]

Autoantigens: Endogenous tissue constituents that have the ability to interact with autoantibodies and cause an immune response. [NIH]

Autoimmune disease: A condition in which the body recognizes its own tissues as foreign and directs an immune response against them. [NIH]

Autoimmune Hepatitis: A liver disease caused when the body's immune system destroys liver cells for no known reason. [NIH]

Autoimmunity: Process whereby the immune system reacts against the body's own tissues. Autoimmunity may produce or be caused by autoimmune diseases. [NIH]

Autopsy: Postmortem examination of the body. [NIH]

Bacteria: Unicellular prokaryotic microorganisms which generally possess rigid cell walls, multiply by cell division, and exhibit three principal forms: round or coccal, rodlike or bacillary, and spiral or spirochetal. [NIH]

Bacterial Physiology: Physiological processes and activities of bacteria. [NIH]

Bactericidal: Substance lethal to bacteria; substance capable of killing bacteria. [NIH]

Bacteriophage: A virus whose host is a bacterial cell; A virus that exclusively infects bacteria. It generally has a protein coat surrounding the genome (DNA or RNA). One of the coliphages most extensively studied is the lambda phage, which is also one of the most important. [NIH]

Basophils: Granular leukocytes characterized by a relatively pale-staining, lobate nucleus and cytoplasm containing coarse dark-staining granules of variable size and stainable by basic dyes. [NIH]

Benign: Not cancerous; does not invade nearby tissue or spread to other parts of the body. [NIH]

Benign tumor: A noncancerous growth that does not invade nearby tissue or spread to other parts of the body. [NIH]

Beta-Galactosidase: A group of enzymes that catalyzes the hydrolysis of terminal, non-reducing beta-D-galactose residues in beta-galactosides. Deficiency of beta-Galactosidase A1 may cause gangliodisosis GM1. EC 3.2.1.23. [NIH]

Beta-Thromboglobulin: A platelet-specific protein which is released when platelets aggregate. Elevated plasma levels have been reported after deep venous thrombosis, pre-eclampsia, myocardial infarction with mural thrombosis, and myeloproliferative disorders. Measurement of beta-thromboglobulin in biological fluids by radioimmunoassay is used for the diagnosis and assessment of progress of thromboembolic disorders. [NIH]

Bilateral: Affecting both the right and left side of body. [NIH]

Bile: An emulsifying agent produced in the liver and secreted into the duodenum. Its composition includes bile acids and salts, cholesterol, and electrolytes. It aids digestion of fats in the duodenum. [NIH]

Bile Acids: Acids made by the liver that work with bile to break down fats. [NIH]

Bile Acids and Salts: Steroid acids and salts. The primary bile acids are derived from cholesterol in the liver and usually conjugated with glycine or taurine. The secondary bile acids are further modified by bacteria in the intestine. They play an important role in the digestion and absorption of fat. They have also been used pharmacologically, especially in the treatment of gallstones. [NIH]

Bile duct: A tube through which bile passes in and out of the liver. [NIH]

Bile Pigments: Pigments that give a characteristic color to bile including: bilirubin, biliverdine, and bilicyanin. [NIH]

Biliary: Having to do with the liver, bile ducts, and/or gallbladder. [NIH]

Biliary Tract: The gallbladder and its ducts. [NIH]

Binding Sites: The reactive parts of a macromolecule that directly participate in its specific combination with another molecule. [NIH]

Bioavailability: The degree to which a drug or other substance becomes available to the target tissue after administration. [EU]

Biochemical: Relating to biochemistry; characterized by, produced by, or involving chemical reactions in living organisms. [EU]

Biological Markers: Measurable and quantifiable biological parameters (e.g., specific enzyme concentration, specific hormone concentration, specific gene phenotype distribution in a population, presence of biological substances) which serve as indices for health- and physiology-related assessments, such as disease risk, psychiatric disorders, environmental exposure and its effects, disease diagnosis, metabolic processes, substance abuse, pregnancy, cell line development, epidemiologic studies, etc. [NIH]

Biological therapy: Treatment to stimulate or restore the ability of the immune system to fight infection and disease. Also used to lessen side effects that may be caused by some cancer treatments. Also known as immunotherapy, biotherapy, or biological response modifier (BRM) therapy. [NIH]

Bioluminescence: The emission of light by living organisms such as the firefly, certain mollusks, beetles, fish, bacteria, fungi and protozoa. [NIH]

Biomarkers: Substances sometimes found in an increased amount in the blood, other body fluids, or tissues and that may suggest the presence of some types of cancer. Biomarkers include CA 125 (ovarian cancer), CA 15-3 (breast cancer), CEA (ovarian, lung, breast, pancreas, and GI tract cancers), and PSA (prostate cancer). Also called tumor markers. [NIH]

Biopsy: Removal and pathologic examination of specimens in the form of small pieces of tissue from the living body. [NIH]

Biosynthesis: The building up of a chemical compound in the physiologic processes of a living organism. [EU]

Biotechnology: Body of knowledge related to the use of organisms, cells or cell-derived constituents for the purpose of developing products which are technically, scientifically and clinically useful. Alteration of biologic function at the molecular level (i.e., genetic engineering) is a central focus; laboratory methods used include transfection and cloning technologies, sequence and structure analysis algorithms, computer databases, and gene and

protein structure function analysis and prediction. [NIH]

Biphasic: Having two phases; having both a sporophytic and a gametophytic phase in the life cycle. [EU]

Bladder: The organ that stores urine. [NIH]

Blast phase: The phase of chronic myelogenous leukemia in which the number of immature, abnormal white blood cells in the bone marrow and blood is extremely high. Also called blast crisis. [NIH]

Blood Cell Count: A count of the number of leukocytes and erythrocytes per unit volume in a sample of venous blood. A complete blood count (CBC) also includes measurement of the hemoglobin, hematocrit, and erythrocyte indices. [NIH]

Blood Coagulation: The process of the interaction of blood coagulation factors that results in an insoluble fibrin clot. [NIH]

Blood Glucose: Glucose in blood. [NIH]

Blood Platelets: Non-nucleated disk-shaped cells formed in the megakaryocyte and found in the blood of all mammals. They are mainly involved in blood coagulation. [NIH]

Blood pressure: The pressure of blood against the walls of a blood vessel or heart chamber. Unless there is reference to another location, such as the pulmonary artery or one of the heart chambers, it refers to the pressure in the systemic arteries, as measured, for example, in the forearm. [NIH]

Blood transfusion: The administration of blood or blood products into a blood vessel. [NIH]

Blood vessel: A tube in the body through which blood circulates. Blood vessels include a network of arteries, arterioles, capillaries, venules, and veins. [NIH]

Blot: To transfer DNA, RNA, or proteins to an immobilizing matrix such as nitrocellulose. [NIH]

Body Fluids: Liquid components of living organisms. [NIH]

Body Mass Index: One of the anthropometric measures of body mass; it has the highest correlation with skinfold thickness or body density. [NIH]

Bone Marrow: The soft tissue filling the cavities of bones. Bone marrow exists in two types, yellow and red. Yellow marrow is found in the large cavities of large bones and consists mostly of fat cells and a few primitive blood cells. Red marrow is a hematopoietic tissue and is the site of production of erythrocytes and granular leukocytes. Bone marrow is made up of a framework of connective tissue containing branching fibers with the frame being filled with marrow cells. [NIH]

Border Disease: Congenital disorder of lambs caused by a virus closely related to or identical with certain strains of bovine viral diarrhea virus. [NIH]

Border Disease Virus: A species of Pestivirus causing a congenital sheep disease characterized by an abnormally hairy birth-coat, tremors, and poor growth. [NIH]

Bowel: The long tube-shaped organ in the abdomen that completes the process of digestion. There is both a small and a large bowel. Also called the intestine. [NIH]

Breast Feeding: The nursing of an infant at the mother's breast. [NIH]

Buccal: Pertaining to or directed toward the cheek. In dental anatomy, used to refer to the buccal surface of a tooth. [EU]

Calcium: A basic element found in nearly all organized tissues. It is a member of the alkaline earth family of metals with the atomic symbol Ca, atomic number 20, and atomic weight 40. Calcium is the most abundant mineral in the body and combines with

phosphorus to form calcium phosphate in the bones and teeth. It is essential for the normal functioning of nerves and muscles and plays a role in blood coagulation (as factor IV) and in many enzymatic processes. [NIH]

Capsid: The outer protein protective shell of a virus, which protects the viral nucleic acid. [NIH]

Capsules: Hard or soft soluble containers used for the oral administration of medicine. [NIH]

Carbohydrate: An aldehyde or ketone derivative of a polyhydric alcohol, particularly of the pentahydric and hexahydric alcohols. They are so named because the hydrogen and oxygen are usually in the proportion to form water, (CH2O)n. The most important carbohydrates are the starches, sugars, celluloses, and gums. They are classified into mono-, di-, tri-, poly- and heterosaccharides. [EU]

Carcinogen: Any substance that causes cancer. [NIH]

Carcinogenesis: The process by which normal cells are transformed into cancer cells. [NIH]

Carcinogenic: Producing carcinoma. [EU]

Carcinoma: Cancer that begins in the skin or in tissues that line or cover internal organs. [NIH]

Cardiac: Having to do with the heart. [NIH]

Cardiolipins: Acidic phospholipids composed of two molecules of phosphatidic acid covalently linked to a molecule of glycerol. They occur primarily in mitochondrial inner membranes and in bacterial plasma membranes. They are the main antigenic components of the Wassermann-type antigen that is used in nontreponemal syphilis serodiagnosis. [NIH]

Cardiovascular: Having to do with the heart and blood vessels. [NIH]

Cardiovascular disease: Any abnormal condition characterized by dysfunction of the heart and blood vessels. CVD includes atherosclerosis (especially coronary heart disease, which can lead to heart attacks), cerebrovascular disease (e.g., stroke), and hypertension (high blood pressure). [NIH]

Carrier State: The condition of harboring an infective organism without manifesting symptoms of infection. The organism must be readily transmissable to another susceptible host. [NIH]

Case report: A detailed report of the diagnosis, treatment, and follow-up of an individual patient. Case reports also contain some demographic information about the patient (for example, age, gender, ethnic origin). [NIH]

Case series: A group or series of case reports involving patients who were given similar treatment. Reports of case series usually contain detailed information about the individual patients. This includes demographic information (for example, age, gender, ethnic origin) and information on diagnosis, treatment, response to treatment, and follow-up after treatment. [NIH]

Case-Control Studies: Studies which start with the identification of persons with a disease of interest and a control (comparison, referent) group without the disease. The relationship of an attribute to the disease is examined by comparing diseased and non-diseased persons with regard to the frequency or levels of the attribute in each group. [NIH]

Caspase: Enzyme released by the cell at a crucial stage in apoptosis in order to shred all cellular proteins. [NIH]

Catalyse: To speed up a chemical reaction. [EU]

Catalytic Domain: The region of an enzyme that interacts with its substrate to cause the enzymatic reaction. [NIH]

Catheterization: Use or insertion of a tubular device into a duct, blood vessel, hollow organ, or body cavity for injecting or withdrawing fluids for diagnostic or therapeutic purposes. It differs from intubation in that the tube here is used to restore or maintain patency in obstructions. [NIH]

Causal: Pertaining to a cause; directed against a cause. [EU]

Celiac Artery: The arterial trunk that arises from the abdominal aorta and after a short course divides into the left gastric, common hepatic and splenic arteries. [NIH]

Cell: The individual unit that makes up all of the tissues of the body. All living things are made up of one or more cells. [NIH]

Cell Cycle: The complex series of phenomena, occurring between the end of one cell division and the end of the next, by which cellular material is divided between daughter cells. [NIH]

Cell Death: The termination of the cell's ability to carry out vital functions such as metabolism, growth, reproduction, responsiveness, and adaptability. [NIH]

Cell Differentiation: Progressive restriction of the developmental potential and increasing specialization of function which takes place during the development of the embryo and leads to the formation of specialized cells, tissues, and organs. [NIH]

Cell Division: The fission of a cell. [NIH]

Cell Fusion: Fusion of somatic cells in vitro or in vivo, which results in somatic cell hybridization. [NIH]

Cell membrane: Cell membrane = plasma membrane. The structure enveloping a cell, enclosing the cytoplasm, and forming a selective permeability barrier; it consists of lipids, proteins, and some carbohydrates, the lipids thought to form a bilayer in which integral proteins are embedded to varying degrees. [EU]

Cell motility: The ability of a cell to move. [NIH]

Cell proliferation: An increase in the number of cells as a result of cell growth and cell division. [NIH]

Cell Respiration: The metabolic process of all living cells (animal and plant) in which oxygen is used to provide a source of energy for the cell. [NIH]

Cell Size: The physical dimensions of a cell. It refers mainly to changes in dimensions correlated with physiological or pathological changes in cells. [NIH]

Cell Survival: The span of viability of a cell characterized by the capacity to perform certain functions such as metabolism, growth, reproduction, some form of responsiveness, and adaptability. [NIH]

Cellulose: A polysaccharide with glucose units linked as in cellobiose. It is the chief constituent of plant fibers, cotton being the purest natural form of the substance. As a raw material, it forms the basis for many derivatives used in chromatography, ion exchange materials, explosives manufacturing, and pharmaceutical preparations. [NIH]

Central Nervous System: The main information-processing organs of the nervous system, consisting of the brain, spinal cord, and meninges. [NIH]

Centrifugation: A method of separating organelles or large molecules that relies upon differential sedimentation through a preformed density gradient under the influence of a gravitational field generated in a centrifuge. [NIH]

Cerebral: Of or pertaining of the cerebrum or the brain. [EU]

Cerebrospinal: Pertaining to the brain and spinal cord. [EU]

Cerebrospinal fluid: CSF. The fluid flowing around the brain and spinal cord. Cerebrospinal fluid is produced in the ventricles in the brain. [NIH]

Cerebrovascular: Pertaining to the blood vessels of the cerebrum, or brain. [EU]

Cerebrum: The largest part of the brain. It is divided into two hemispheres, or halves, called the cerebral hemispheres. The cerebrum controls muscle functions of the body and also controls speech, emotions, reading, writing, and learning. [NIH]

Cervical: Relating to the neck, or to the neck of any organ or structure. Cervical lymph nodes are located in the neck; cervical cancer refers to cancer of the uterine cervix, which is the lower, narrow end (the "neck") of the uterus. [NIH]

Cervix: The lower, narrow end of the uterus that forms a canal between the uterus and vagina. [NIH]

Cesarean Section: Extraction of the fetus by means of abdominal hysterotomy. [NIH]

Character: In current usage, approximately equivalent to personality. The sum of the relatively fixed personality traits and habitual modes of response of an individual. [NIH]

Chemical Warfare: Tactical warfare using incendiary mixtures, smokes, or irritant, burning, or asphyxiating gases. [NIH]

Chemical Warfare Agents: Chemicals that are used to cause the disturbance, disease, or death of humans during war. [NIH]

Chemokines: Class of pro-inflammatory cytokines that have the ability to attract and activate leukocytes. They can be divided into at least three structural branches: C (chemokines, C), CC (chemokines, CC), and CXC (chemokines, CXC), according to variations in a shared cysteine motif. [NIH]

Chemotactic Factors: Chemical substances that attract or repel cells or organisms. The concept denotes especially those factors released as a result of tissue injury, invasion, or immunologic activity, that attract leukocytes, macrophages, or other cells to the site of infection or insult. [NIH]

Chemotherapy: Treatment with anticancer drugs. [NIH]

Chimera: An individual that contains cell populations derived from different zygotes. [NIH]

Chin: The anatomical frontal portion of the mandible, also known as the mentum, that contains the line of fusion of the two separate halves of the mandible (symphysis menti). This line of fusion divides inferiorly to enclose a triangular area called the mental protuberance. On each side, inferior to the second premolar tooth, is the mental foramen for the passage of blood vessels and a nerve. [NIH]

Chiropractic: A system of treating bodily disorders by manipulation of the spine and other parts, based on the belief that the cause is the abnormal functioning of a nerve. [NIH]

Chlorine: A greenish-yellow, diatomic gas that is a member of the halogen family of elements. It has the atomic symbol Cl, atomic number 17, and atomic weight 70.906. It is a powerful irritant that can cause fatal pulmonary edema. Chlorine is used in manufacturing, as a reagent in synthetic chemistry, for water purification, and in the production of chlorinated lime, which is used in fabric bleaching. [NIH]

Cholangitis: Inflammation of a bile duct. [NIH]

Cholestasis: Impairment of biliary flow at any level from the hepatocyte to Vater's ampulla. [NIH]

Cholesterol: The principal sterol of all higher animals, distributed in body tissues, especially the brain and spinal cord, and in animal fats and oils. [NIH]

Cholesterol Esters: Fatty acid esters of cholesterol which constitute about two-thirds of the

cholesterol in the plasma. The accumulation of cholesterol esters in the arterial intima is a characteristic feature of atherosclerosis. [NIH]

Chorioretinitis: Inflammation of the choroid in which the sensory retina becomes edematous and opaque. The inflammatory cells and exudate may burst through the sensory retina to cloud the vitreous body. [NIH]

Choroid: The thin, highly vascular membrane covering most of the posterior of the eye between the retina and sclera. [NIH]

Chromatin: The material of chromosomes. It is a complex of DNA, histones, and nonhistone proteins (chromosomal proteins, non-histone) found within the nucleus of a cell. [NIH]

Chromosomal: Pertaining to chromosomes. [EU]

Chromosome: Part of a cell that contains genetic information. Except for sperm and eggs, all human cells contain 46 chromosomes. [NIH]

Chronic: A disease or condition that persists or progresses over a long period of time. [NIH]

Chronic Disease: Disease or ailment of long duration. [NIH]

Chronic lymphocytic leukemia: A slowly progressing disease in which too many white blood cells (called lymphocytes) are found in the body. [NIH]

Chronic myelogenous leukemia: CML. A slowly progressing disease in which too many white blood cells are made in the bone marrow. Also called chronic myeloid leukemia or chronic granulocytic leukemia. [NIH]

Chronic phase: Refers to the early stages of chronic myelogenous leukemia or chronic lymphocytic leukemia. The number of mature and immature abnormal white blood cells in the bone marrow and blood is higher than normal, but lower than in the accelerated or blast phase. [NIH]

Chylomicrons: A class of lipoproteins that carry dietary cholesterol and triglycerides from the small intestines to the tissues. [NIH]

Circumcision: Excision of the prepuce or part of it. [NIH]

Cirrhosis: A type of chronic, progressive liver disease. [NIH]

CIS: Cancer Information Service. The CIS is the National Cancer Institute's link to the public, interpreting and explaining research findings in a clear and understandable manner, and providing personalized responses to specific questions about cancer. Access the CIS by calling 1-800-4-CANCER, or by using the Web site at http://cis.nci.nih.gov. [NIH]

Cleave: A double-stranded cut in DNA with a restriction endonuclease. [NIH]

Clinical Medicine: The study and practice of medicine by direct examination of the patient. [NIH]

Clinical study: A research study in which patients receive treatment in a clinic or other medical facility. Reports of clinical studies can contain results for single patients (case reports) or many patients (case series or clinical trials). [NIH]

Clinical trial: A research study that tests how well new medical treatments or other interventions work in people. Each study is designed to test new methods of screening, prevention, diagnosis, or treatment of a disease. [NIH]

Clone: The term "clone" has acquired a new meaning. It is applied specifically to the bits of inserted foreign DNA in the hybrid molecules of the population. Each inserted segment originally resided in the DNA of a complex genome amid millions of other DNA segment. [NIH]

Cloning: The production of a number of genetically identical individuals; in genetic engineering, a process for the efficient replication of a great number of identical DNA

molecules. [NIH]

Coca: Any of several South American shrubs of the Erythroxylon genus (and family) that yield cocaine; the leaves are chewed with alum for CNS stimulation. [NIH]

Cocaine: An alkaloid ester extracted from the leaves of plants including coca. It is a local anesthetic and vasoconstrictor and is clinically used for that purpose, particularly in the eye, ear, nose, and throat. It also has powerful central nervous system effects similar to the amphetamines and is a drug of abuse. Cocaine, like amphetamines, acts by multiple mechanisms on brain catecholaminergic neurons; the mechanism of its reinforcing effects is thought to involve inhibition of dopamine uptake. [NIH]

Codon: A set of three nucleotides in a protein coding sequence that specifies individual amino acids or a termination signal (codon, terminator). Most codons are universal, but some organisms do not produce the transfer RNAs (RNA, transfer) complementary to all codons. These codons are referred to as unassigned codons (codons, nonsense). [NIH]

Cofactor: A substance, microorganism or environmental factor that activates or enhances the action of another entity such as a disease-causing agent. [NIH]

Cognitive restructuring: A method of identifying and replacing fear-promoting, irrational beliefs with more realistic and functional ones. [NIH]

Cohort Studies: Studies in which subsets of a defined population are identified. These groups may or may not be exposed to factors hypothesized to influence the probability of the occurrence of a particular disease or other outcome. Cohorts are defined populations which, as a whole, are followed in an attempt to determine distinguishing subgroup characteristics. [NIH]

Colchicine: A major alkaloid from Colchicum autumnale L. and found also in other Colchicum species. Its primary therapeutic use is in the treatment of gout, but it has been used also in the therapy of familial Mediterranean fever (periodic disease). [NIH]

Collagen: A polypeptide substance comprising about one third of the total protein in mammalian organisms. It is the main constituent of skin, connective tissue, and the organic substance of bones and teeth. Different forms of collagen are produced in the body but all consist of three alpha-polypeptide chains arranged in a triple helix. Collagen is differentiated from other fibrous proteins, such as elastin, by the content of proline, hydroxyproline, and hydroxylysine; by the absence of tryptophan; and particularly by the high content of polar groups which are responsible for its swelling properties. [NIH]

Colloidal: Of the nature of a colloid. [EU]

Colon: The long, coiled, tubelike organ that removes water from digested food. The remaining material, solid waste called stool, moves through the colon to the rectum and leaves the body through the anus. [NIH]

Comorbidity: The presence of co-existing or additional diseases with reference to an initial diagnosis or with reference to the index condition that is the subject of study. Comorbidity may affect the ability of affected individuals to function and also their survival; it may be used as a prognostic indicator for length of hospital stay, cost factors, and outcome or survival. [NIH]

Complement: A term originally used to refer to the heat-labile factor in serum that causes immune cytolysis, the lysis of antibody-coated cells, and now referring to the entire functionally related system comprising at least 20 distinct serum proteins that is the effector not only of immune cytolysis but also of other biologic functions. Complement activation occurs by two different sequences, the classic and alternative pathways. The proteins of the classic pathway are termed 'components of complement' and are designated by the symbols C1 through C9. C1 is a calcium-dependent complex of three distinct proteins C1q, C1r and

C1s. The proteins of the alternative pathway (collectively referred to as the properdin system) and complement regulatory proteins are known by semisystematic or trivial names. Fragments resulting from proteolytic cleavage of complement proteins are designated with lower-case letter suffixes, e.g., C3a. Inactivated fragments may be designated with the suffix 'i', e.g. C3bi. Activated components or complexes with biological activity are designated by a bar over the symbol e.g. C1 or C4b,2a. The classic pathway is activated by the binding of C1 to classic pathway activators, primarily antigen-antibody complexes containing IgM, IgG1, IgG3; C1q binds to a single IgM molecule or two adjacent IgG molecules. The alternative pathway can be activated by IgA immune complexes and also by nonimmunologic materials including bacterial endotoxins, microbial polysaccharides, and cell walls. Activation of the classic pathway triggers an enzymatic cascade involving C1, C4, C2 and C3; activation of the alternative pathway triggers a cascade involving C3 and factors B, D and P. Both result in the cleavage of C5 and the formation of the membrane attack complex. Complement activation also results in the formation of many biologically active complement fragments that act as anaphylatoxins, opsonins, or chemotactic factors. [EU]

Complement 1: The first complement component to act in the cytolysis reaction. It is a trimolecular complex held together with Ca ions and, when activated, has esterase activity which initiates the next step in the sequence. [NIH]

Complement 4: The second component to react in the complement sequence. It is a beta-globulin with a sedimentation coefficient of 18.7, a molecular weight of 240,000 and a serum concentration of 430 micrograms/ml. It is activated by complement 1 and serves as a receptor for C2. [NIH]

Complementary and alternative medicine: CAM. Forms of treatment that are used in addition to (complementary) or instead of (alternative) standard treatments. These practices are not considered standard medical approaches. CAM includes dietary supplements, megadose vitamins, herbal preparations, special teas, massage therapy, magnet therapy, spiritual healing, and meditation. [NIH]

Complementary medicine: Practices not generally recognized by the medical community as standard or conventional medical approaches and used to enhance or complement the standard treatments. Complementary medicine includes the taking of dietary supplements, megadose vitamins, and herbal preparations; the drinking of special teas; and practices such as massage therapy, magnet therapy, spiritual healing, and meditation. [NIH]

Compliance: Distensibility measure of a chamber such as the lungs (lung compliance) or bladder. Compliance is expressed as a change in volume per unit change in pressure. [NIH]

Computational Biology: A field of biology concerned with the development of techniques for the collection and manipulation of biological data, and the use of such data to make biological discoveries or predictions. This field encompasses all computational methods and theories applicable to molecular biology and areas of computer-based techniques for solving biological problems including manipulation of models and datasets. [NIH]

Computed tomography: CT scan. A series of detailed pictures of areas inside the body, taken from different angles; the pictures are created by a computer linked to an x-ray machine. Also called computerized tomography and computerized axial tomography (CAT) scan. [NIH]

Computerized axial tomography: A series of detailed pictures of areas inside the body, taken from different angles; the pictures are created by a computer linked to an x-ray machine. Also called CAT scan, computed tomography (CT scan), or computerized tomography. [NIH]

Computerized tomography: A series of detailed pictures of areas inside the body, taken from different angles; the pictures are created by a computer linked to an x-ray machine.

Also called computerized axial tomography (CAT) scan and computed tomography (CT scan). [NIH]

Conception: The onset of pregnancy, marked by implantation of the blastocyst; the formation of a viable zygote. [EU]

Concomitant: Accompanying; accessory; joined with another. [EU]

Condoms: A sheath that is worn over the penis during sexual behavior in order to prevent pregnancy or spread of sexually transmitted disease. [NIH]

Conjunctiva: The mucous membrane that lines the inner surface of the eyelids and the anterior part of the sclera. [NIH]

Connective Tissue: Tissue that supports and binds other tissues. It consists of connective tissue cells embedded in a large amount of extracellular matrix. [NIH]

Connective Tissue: Tissue that supports and binds other tissues. It consists of connective tissue cells embedded in a large amount of extracellular matrix. [NIH]

Connective Tissue Diseases: A heterogeneous group of disorders, some hereditary, others acquired, characterized by abnormal structure or function of one or more of the elements of connective tissue, i.e., collagen, elastin, or the mucopolysaccharides. [NIH]

Consciousness: Sense of awareness of self and of the environment. [NIH]

Consensus Sequence: A theoretical representative nucleotide or amino acid sequence in which each nucleotide or amino acid is the one which occurs most frequently at that site in the different sequences which occur in nature. The phrase also refers to an actual sequence which approximates the theoretical consensus. A known conserved sequence set is represented by a consensus sequence. Commonly observed supersecondary protein structures (amino acid motifs) are often formed by conserved sequences. [NIH]

Conserved Sequence: A sequence of amino acids in a polypeptide or of nucleotides in DNA or RNA that is similar across multiple species. A known set of conserved sequences is represented by a consensus sequence. Amino acid motifs are often composed of conserved sequences. [NIH]

Constitutional: 1. Affecting the whole constitution of the body; not local. 2. Pertaining to the constitution. [EU]

Constriction: The act of constricting. [NIH]

Contamination: The soiling or pollution by inferior material, as by the introduction of organisms into a wound, or sewage into a stream. [EU]

Continuum: An area over which the vegetation or animal population is of constantly changing composition so that homogeneous, separate communities cannot be distinguished. [NIH]

Contraindications: Any factor or sign that it is unwise to pursue a certain kind of action or treatment, e. g. giving a general anesthetic to a person with pneumonia. [NIH]

Control group: In a clinical trial, the group that does not receive the new treatment being studied. This group is compared to the group that receives the new treatment, to see if the new treatment works. [NIH]

Controlled study: An experiment or clinical trial that includes a comparison (control) group. [NIH]

Conventional therapy: A currently accepted and widely used treatment for a certain type of disease, based on the results of past research. Also called conventional treatment. [NIH]

Conventional treatment: A currently accepted and widely used treatment for a certain type of disease, based on the results of past research. Also called conventional therapy. [NIH]

Coordination: Muscular or motor regulation or the harmonious cooperation of muscles or groups of muscles, in a complex action or series of actions. [NIH]

Coronary: Encircling in the manner of a crown; a term applied to vessels; nerves, ligaments, etc. The term usually denotes the arteries that supply the heart muscle and, by extension, a pathologic involvement of them. [EU]

Coronary heart disease: A type of heart disease caused by narrowing of the coronary arteries that feed the heart, which needs a constant supply of oxygen and nutrients carried by the blood in the coronary arteries. When the coronary arteries become narrowed or clogged by fat and cholesterol deposits and cannot supply enough blood to the heart, CHD results. [NIH]

Coronary Thrombosis: Presence of a thrombus in a coronary artery, often causing a myocardial infarction. [NIH]

Cowpox: A mild, eruptive skin disease of milk cows caused by cowpox virus, with lesions occurring principally on the udder and teats. Human infection may occur while milking an infected animal. [NIH]

Cowpox Virus: A species of orthopoxvirus that is the etiologic agent of cowpox. It is closely related to but antigenically different from vaccina virus. [NIH]

Crossing-over: The exchange of corresponding segments between chromatids of homologous chromosomes during meiosia, forming a chiasma. [NIH]

Cryoglobulinemia: A condition characterized by the presence of abnormal or abnormal quantities of cryoglobulins in the blood. They are precipitated into the microvasculature on exposure to cold and cause restricted blood flow in exposed areas. [NIH]

Crystallization: The formation of crystals; conversion to a crystalline form. [EU]

Cultured cells: Animal or human cells that are grown in the laboratory. [NIH]

Curative: Tending to overcome disease and promote recovery. [EU]

Cutaneous: Having to do with the skin. [NIH]

Cyclic: Pertaining to or occurring in a cycle or cycles; the term is applied to chemical compounds that contain a ring of atoms in the nucleus. [EU]

Cysteine: A thiol-containing non-essential amino acid that is oxidized to form cystine. [NIH]

Cytogenetics: A branch of genetics which deals with the cytological and molecular behavior of genes and chromosomes during cell division. [NIH]

Cytokine: Small but highly potent protein that modulates the activity of many cell types, including T and B cells. [NIH]

Cytomegalovirus: A genus of the family Herpesviridae, subfamily Betaherpesvirinae, infecting the salivary glands, liver, spleen, lungs, eyes, and other organs, in which they produce characteristically enlarged cells with intranuclear inclusions. Infection with Cytomegalovirus is also seen as an opportunistic infection in AIDS. [NIH]

Cytoplasm: The protoplasm of a cell exclusive of that of the nucleus; it consists of a continuous aqueous solution (cytosol) and the organelles and inclusions suspended in it (phaneroplasm), and is the site of most of the chemical activities of the cell. [EU]

Cytotoxic: Cell-killing. [NIH]

Cytotoxicity: Quality of being capable of producing a specific toxic action upon cells of special organs. [NIH]

Data Collection: Systematic gathering of data for a particular purpose from various sources, including questionnaires, interviews, observation, existing records, and electronic devices.

The process is usually preliminary to statistical analysis of the data. [NIH]

De novo: In cancer, the first occurrence of cancer in the body. [NIH]

Decompensation: Failure of compensation; cardiac decompensation is marked by dyspnea, venous engorgement, and edema. [EU]

Decontamination: The removal of contaminating material, such as radioactive materials, biological materials, or chemical warfare agents, from a person or object. [NIH]

Degenerative: Undergoing degeneration : tending to degenerate; having the character of or involving degeneration; causing or tending to cause degeneration. [EU]

Deletion: A genetic rearrangement through loss of segments of DNA (chromosomes), bringing sequences, which are normally separated, into close proximity. [NIH]

Dementia: An acquired organic mental disorder with loss of intellectual abilities of sufficient severity to interfere with social or occupational functioning. The dysfunction is multifaceted and involves memory, behavior, personality, judgment, attention, spatial relations, language, abstract thought, and other executive functions. The intellectual decline is usually progressive, and initially spares the level of consciousness. [NIH]

Denaturation: Rupture of the hydrogen bonds by heating a DNA solution and then cooling it rapidly causes the two complementary strands to separate. [NIH]

Dendrites: Extensions of the nerve cell body. They are short and branched and receive stimuli from other neurons. [NIH]

Dendritic: 1. Branched like a tree. 2. Pertaining to or possessing dendrites. [EU]

Dendritic cell: A special type of antigen-presenting cell (APC) that activates T lymphocytes. [NIH]

Dengue Virus: A species of the genus Flavivirus which causes an acute febrile and sometimes hemorrhagic disease in man. Dengue is mosquito-borne and four serotypes are known. [NIH]

Density: The logarithm to the base 10 of the opacity of an exposed and processed film. [NIH]

Deoxyguanosine: A nucleoside consisting of the base guanine and the sugar deoxyribose. [NIH]

Dermal: Pertaining to or coming from the skin. [NIH]

Desensitization: The prevention or reduction of immediate hypersensitivity reactions by administration of graded doses of allergen; called also hyposensitization and immunotherapy. [EU]

Detergents: Purifying or cleansing agents, usually salts of long-chain aliphatic bases or acids, that exert cleansing (oil-dissolving) and antimicrobial effects through a surface action that depends on possessing both hydrophilic and hydrophobic properties. [NIH]

Developed Countries: Countries that have reached a level of economic achievement through an increase of production, per capita income and consumption, and utilization of natural and human resources. [NIH]

Developing Countries: Countries in the process of change directed toward economic growth, that is, an increase in production, per capita consumption, and income. The process of economic growth involves better utilization of natural and human resources, which results in a change in the social, political, and economic structures. [NIH]

Dextran Sulfate: Long-chain polymer of glucose containing 17-20% sulfur. It has been used as an anticoagulant and also has been shown to inhibit the binding of HIV-1 to CD4+ T-lymphocytes. It is commonly used as both an experimental and clinical laboratory reagent and has been investigated for use as an antiviral agent, in the treatment of hypolipidemia,

and for the prevention of free radical damage, among other applications. [NIH]

Diabetes Mellitus: A heterogeneous group of disorders that share glucose intolerance in common. [NIH]

Diagnostic procedure: A method used to identify a disease. [NIH]

Dialysate: A cleansing liquid used in the two major forms of dialysis--hemodialysis and peritoneal dialysis. [NIH]

Dialyzer: A part of the hemodialysis machine. (See hemodialysis under dialysis.) The dialyzer has two sections separated by a membrane. One section holds dialysate. The other holds the patient's blood. [NIH]

Diarrhea: Passage of excessively liquid or excessively frequent stools. [NIH]

Diarrhoea: Abnormal frequency and liquidity of faecal discharges. [EU]

Diathesis: A constitution or condition of the body which makes the tissues react in special ways to certain extrinsic stimuli and thus tends to make the person more than usually susceptible to certain diseases. [EU]

Diffusion: The tendency of a gas or solute to pass from a point of higher pressure or concentration to a point of lower pressure or concentration and to distribute itself throughout the available space; a major mechanism of biological transport. [NIH]

Digestion: The process of breakdown of food for metabolism and use by the body. [NIH]

Digestive system: The organs that take in food and turn it into products that the body can use to stay healthy. Waste products the body cannot use leave the body through bowel movements. The digestive system includes the salivary glands, mouth, esophagus, stomach, liver, pancreas, gallbladder, small and large intestines, and rectum. [NIH]

Digestive tract: The organs through which food passes when food is eaten. These organs are the mouth, esophagus, stomach, small and large intestines, and rectum. [NIH]

Dilution: A diluted or attenuated medicine; in homeopathy, the diffusion of a given quantity of a medicinal agent in ten or one hundred times the same quantity of water. [NIH]

Dimethyl: A volatile metabolite of the amino acid methionine. [NIH]

Diploid: Having two sets of chromosomes. [NIH]

Direct: 1. Straight; in a straight line. 2. Performed immediately and without the intervention of subsidiary means. [EU]

Discrete: Made up of separate parts or characterized by lesions which do not become blended; not running together; separate. [NIH]

Disease Transmission: The transmission of infectious disease or pathogens. When transmission is within the same species, the mode can be horizontal (disease transmission, horizontal) or vertical (disease transmission, vertical). [NIH]

Disease Transmission, Horizontal: The transmission of infectious disease or pathogens from one individual to another in the same generation. [NIH]

Disease Transmission, Vertical: The transmission of infectious disease or pathogens from one generation to another. It includes transmission in utero or intrapartum by exposure to blood and secretions, and postpartum exposure via breastfeeding. [NIH]

Disinfectant: An agent that disinfects; applied particularly to agents used on inanimate objects. [EU]

Disinfection: Rendering pathogens harmless through the use of heat, antiseptics, antibacterial agents, etc. [NIH]

Disparity: Failure of the two retinal images of an object to fall on corresponding retinal

points. [NIH]

Dissection: Cutting up of an organism for study. [NIH]

Dissociation: 1. The act of separating or state of being separated. 2. The separation of a molecule into two or more fragments (atoms, molecules, ions, or free radicals) produced by the absorption of light or thermal energy or by solvation. 3. In psychology, a defense mechanism in which a group of mental processes are segregated from the rest of a person's mental activity in order to avoid emotional distress, as in the dissociative disorders (q.v.), or in which an idea or object is segregated from its emotional significance; in the first sense it is roughly equivalent to splitting, in the second, to isolation. 4. A defect of mental integration in which one or more groups of mental processes become separated off from normal consciousness and, thus separated, function as a unitary whole. [EU]

Distal: Remote; farther from any point of reference; opposed to proximal. In dentistry, used to designate a position on the dental arch farther from the median line of the jaw. [EU]

Domesticated: Species in which the evolutionary process has been influenced by humans to meet their needs. [NIH]

Dopamine: An endogenous catecholamine and prominent neurotransmitter in several systems of the brain. In the synthesis of catecholamines from tyrosine, it is the immediate precursor to norepinephrine and epinephrine. Dopamine is a major transmitter in the extrapyramidal system of the brain, and important in regulating movement. A family of dopaminergic receptor subtypes mediate its action. Dopamine is used pharmacologically for its direct (beta adrenergic agonist) and indirect (adrenergic releasing) sympathomimetic effects including its actions as an inotropic agent and as a renal vasodilator. [NIH]

Dose-dependent: Refers to the effects of treatment with a drug. If the effects change when the dose of the drug is changed, the effects are said to be dose dependent. [NIH]

Double-blind: Pertaining to a clinical trial or other experiment in which neither the subject nor the person administering treatment knows which treatment any particular subject is receiving. [EU]

Drug Combinations: Single preparations containing two or more active agents, for the purpose of their concurrent administration as a fixed dose mixture. It is differentiated from combination drug therapy in which two or more drugs are administered separately for a combined effect. [NIH]

Drug Design: The molecular designing of drugs for specific purposes (such as DNA-binding, enzyme inhibition, anti-cancer efficacy, etc.) based on knowledge of molecular properties such as activity of functional groups, molecular geometry, and electronic structure, and also on information cataloged on analogous molecules. Drug design is generally computer-assisted molecular modeling and does not include pharmacokinetics, dosage analysis, or drug administration analysis. [NIH]

Drug Interactions: The action of a drug that may affect the activity, metabolism, or toxicity of another drug. [NIH]

Drug Resistance: Diminished or failed response of an organism, disease or tissue to the intended effectiveness of a chemical or drug. It should be differentiated from drug tolerance which is the progressive diminution of the susceptibility of a human or animal to the effects of a drug, as a result of continued administration. [NIH]

Drug Tolerance: Progressive diminution of the susceptibility of a human or animal to the effects of a drug, resulting from its continued administration. It should be differentiated from drug resistance wherein an organism, disease, or tissue fails to respond to the intended effectiveness of a chemical or drug. It should also be differentiated from maximum tolerated dose and no-observed-adverse-effect level. [NIH]

Duct: A tube through which body fluids pass. [NIH]

Duodenum: The first part of the small intestine. [NIH]

Dyslipidemia: Disorders in the lipoprotein metabolism; classified as hypercholesterolemia, hypertriglyceridemia, combined hyperlipidemia, and low levels of high-density lipoprotein (HDL) cholesterol. All of the dyslipidemias can be primary or secondary. Both elevated levels of low-density lipoprotein (LDL) cholesterol and low levels of HDL cholesterol predispose to premature atherosclerosis. [NIH]

Dysplasia: Cells that look abnormal under a microscope but are not cancer. [NIH]

Dyspnea: Difficult or labored breathing. [NIH]

Edema: Excessive amount of watery fluid accumulated in the intercellular spaces, most commonly present in subcutaneous tissue. [NIH]

Effector: It is often an enzyme that converts an inactive precursor molecule into an active second messenger. [NIH]

Efficacy: The extent to which a specific intervention, procedure, regimen, or service produces a beneficial result under ideal conditions. Ideally, the determination of efficacy is based on the results of a randomized control trial. [NIH]

Effusion: The escape of fluid into a part or tissue, as an exudation or a transudation. [EU]

Ejaculation: The release of semen through the penis during orgasm. [NIH]

Elastic: Susceptible of resisting and recovering from stretching, compression or distortion applied by a force. [EU]

Electrolytes: Substances that break up into ions (electrically charged particles) when they are dissolved in body fluids or water. Some examples are sodium, potassium, chloride, and calcium. Electrolytes are primarily responsible for the movement of nutrients into cells, and the movement of wastes out of cells. [NIH]

Electrons: Stable elementary particles having the smallest known negative charge, present in all elements; also called negatrons. Positively charged electrons are called positrons. The numbers, energies and arrangement of electrons around atomic nuclei determine the chemical identities of elements. Beams of electrons are called cathode rays or beta rays, the latter being a high-energy biproduct of nuclear decay. [NIH]

Electrophoresis: An electrochemical process in which macromolecules or colloidal particles with a net electric charge migrate in a solution under the influence of an electric current. [NIH]

Elementary Particles: Individual components of atoms, usually subatomic; subnuclear particles are usually detected only when the atomic nucleus decays and then only transiently, as most of them are unstable, often yielding pure energy without substance, i.e., radiation. [NIH]

Emaciation: Clinical manifestation of excessive leanness usually caused by disease or a lack of nutrition. [NIH]

Emboli: Bit of foreign matter which enters the blood stream at one point and is carried until it is lodged or impacted in an artery and obstructs it. It may be a blood clot, an air bubble, fat or other tissue, or clumps of bacteria. [NIH]

Embryo: The prenatal stage of mammalian development characterized by rapid morphological changes and the differentiation of basic structures. [NIH]

Emergency Medical Technicians: Paramedical personnel trained to provide basic emergency care and life support under the supervision of physicians and/or nurses. These services may be carried out at the site of the emergency, in the ambulance, or in a health care

institution. [NIH]

Encephalitis: Inflammation of the brain due to infection, autoimmune processes, toxins, and other conditions. Viral infections (see encephalitis, viral) are a relatively frequent cause of this condition. [NIH]

Encephalitis, Viral: Inflammation of brain parenchymal tissue as a result of viral infection. Encephalitis may occur as primary or secondary manifestation of Togaviridae infections; Herpesviridae infections; Adenoviridae infections; Flaviviridae infections; Bunyaviridae infections; Picornaviridae infections; Paramyxoviridae infections; Orthomyxoviridae infections; Retroviridae infections; and Arenaviridae infections. [NIH]

Endemic: Present or usually prevalent in a population or geographical area at all times; said of a disease or agent. Called also endemial. [EU]

Endocytosis: Cellular uptake of extracellular materials within membrane-limited vacuoles or microvesicles. Endosomes play a central role in endocytosis. [NIH]

Endogenous: Produced inside an organism or cell. The opposite is external (exogenous) production. [NIH]

Endopeptidases: A subclass of peptide hydrolases. They are classified primarily by their catalytic mechanism. Specificity is used only for identification of individual enzymes. They comprise the serine endopeptidases, EC 3.4.21; cysteine endopeptidases, EC 3.4.22; aspartic endopeptidases, EC 3.4.23, metalloendopeptidases, EC 3.4.24; and a group of enzymes yet to be assigned to any of the above sub-classes, EC 3.4.99. EC 3.4.-. [NIH]

Endoscopy: Endoscopic examination, therapy or surgery performed on interior parts of the body. [NIH]

Endothelial cell: The main type of cell found in the inside lining of blood vessels, lymph vessels, and the heart. [NIH]

Endothelium: A layer of epithelium that lines the heart, blood vessels (endothelium, vascular), lymph vessels (endothelium, lymphatic), and the serous cavities of the body. [NIH]

Endothelium, Lymphatic: Unbroken cellular lining (intima) of the lymph vessels (e.g., the high endothelial lymphatic venules). It is more permeable than vascular endothelium, lacking selective absorption and functioning mainly to remove plasma proteins that have filtered through the capillaries into the tissue spaces. [NIH]

Endothelium, Vascular: Single pavement layer of cells which line the luminal surface of the entire vascular system and regulate the transport of macromolecules and blood components from interstitium to lumen; this function has been most intensively studied in the blood capillaries. [NIH]

Endotoxemia: A condition characterized by the presence of endotoxins in the blood. If endotoxemia is the result of gram-negative rod-shaped bacteria, shock may occur. [NIH]

Endotoxins: Toxins closely associated with the living cytoplasm or cell wall of certain microorganisms, which do not readily diffuse into the culture medium, but are released upon lysis of the cells. [NIH]

Enhancers: Transcriptional element in the virus genome. [NIH]

Environmental Exposure: The exposure to potentially harmful chemical, physical, or biological agents in the environment or to environmental factors that may include ionizing radiation, pathogenic organisms, or toxic chemicals. [NIH]

Environmental Health: The science of controlling or modifying those conditions, influences, or forces surrounding man which relate to promoting, establishing, and maintaining health. [NIH]

Enzymatic: Phase where enzyme cuts the precursor protein. [NIH]

Enzyme: A protein that speeds up chemical reactions in the body. [NIH]

Enzyme Inhibitors: Compounds or agents that combine with an enzyme in such a manner as to prevent the normal substrate-enzyme combination and the catalytic reaction. [NIH]

Enzyme-Linked Immunosorbent Assay: An immunoassay utilizing an antibody labeled with an enzyme marker such as horseradish peroxidase. While either the enzyme or the antibody is bound to an immunosorbent substrate, they both retain their biologic activity; the change in enzyme activity as a result of the enzyme-antibody-antigen reaction is proportional to the concentration of the antigen and can be measured spectrophotometrically or with the naked eye. Many variations of the method have been developed. [NIH]

Eosinophils: Granular leukocytes with a nucleus that usually has two lobes connected by a slender thread of chromatin, and cytoplasm containing coarse, round granules that are uniform in size and stainable by eosin. [NIH]

Epidemic: Occurring suddenly in numbers clearly in excess of normal expectancy; said especially of infectious diseases but applied also to any disease, injury, or other health-related event occurring in such outbreaks. [EU]

Epidemiologic Studies: Studies designed to examine associations, commonly, hypothesized causal relations. They are usually concerned with identifying or measuring the effects of risk factors or exposures. The common types of analytic study are case-control studies, cohort studies, and cross-sectional studies. [NIH]

Epidemiological: Relating to, or involving epidemiology. [EU]

Epidermal: Pertaining to or resembling epidermis. Called also epidermic or epidermoid. [EU]

Epidermis: Nonvascular layer of the skin. It is made up, from within outward, of five layers: 1) basal layer (stratum basale epidermidis); 2) spinous layer (stratum spinosum epidermidis); 3) granular layer (stratum granulosum epidermidis); 4) clear layer (stratum lucidum epidermidis); and 5) horny layer (stratum corneum epidermidis). [NIH]

Epigastric: Having to do with the upper middle area of the abdomen. [NIH]

Epinephrine: The active sympathomimetic hormone from the adrenal medulla in most species. It stimulates both the alpha- and beta- adrenergic systems, causes systemic vasoconstriction and gastrointestinal relaxation, stimulates the heart, and dilates bronchi and cerebral vessels. It is used in asthma and cardiac failure and to delay absorption of local anesthetics. [NIH]

Epithelial: Refers to the cells that line the internal and external surfaces of the body. [NIH]

Epithelial Cells: Cells that line the inner and outer surfaces of the body. [NIH]

Epithelium: One or more layers of epithelial cells, supported by the basal lamina, which covers the inner or outer surfaces of the body. [NIH]

Epitope: A molecule or portion of a molecule capable of binding to the combining site of an antibody. For every given antigenic determinant, the body can construct a variety of antibody-combining sites, some of which fit almost perfectly, and others which barely fit. [NIH]

Epitope Mapping: Methods used for studying the interactions of antibodies with specific regions of protein antigens. Important applications of epitope mapping are found within the area of immunochemistry. [NIH]

Epoetin alfa: A colony-stimulating factor that is made in the laboratory. It increases the production of red blood cells. [NIH]

ERV: The expiratory reserve volume is the largest volume of gas that can be expired from the end-expiratory level. [NIH]

Erythrocytes: Red blood cells. Mature erythrocytes are non-nucleated, biconcave disks containing hemoglobin whose function is to transport oxygen. [NIH]

Erythropoietin: Glycoprotein hormone, secreted chiefly by the kidney in the adult and the liver in the fetus, that acts on erythroid stem cells of the bone marrow to stimulate proliferation and differentiation. [NIH]

Esophagus: The muscular tube through which food passes from the throat to the stomach. [NIH]

Ethanol: A clear, colorless liquid rapidly absorbed from the gastrointestinal tract and distributed throughout the body. It has bactericidal activity and is used often as a topical disinfectant. It is widely used as a solvent and preservative in pharmaceutical preparations as well as serving as the primary ingredient in alcoholic beverages. [NIH]

Eukaryotic Cells: Cells of the higher organisms, containing a true nucleus bounded by a nuclear membrane. [NIH]

Excipient: Any more or less inert substance added to a prescription in order to confer a suitable consistency or form to the drug; a vehicle. [EU]

Excitation: An act of irritation or stimulation or of responding to a stimulus; the addition of energy, as the excitation of a molecule by absorption of photons. [EU]

Exocrine: Secreting outwardly, via a duct. [EU]

Exogenous: Developed or originating outside the organism, as exogenous disease. [EU]

Expiratory: The volume of air which leaves the breathing organs in each expiration. [NIH]

Expiratory Reserve Volume: The extra volume of air that can be expired with maximum effort beyond the level reached at the end of a normal, quiet expiration. Common abbreviation is ERV. [NIH]

Extensor: A muscle whose contraction tends to straighten a limb; the antagonist of a flexor. [NIH]

Extracellular: Outside a cell or cells. [EU]

Extraction: The process or act of pulling or drawing out. [EU]

Extrapyramidal: Outside of the pyramidal tracts. [EU]

Extravasation: A discharge or escape, as of blood, from a vessel into the tissues. [EU]

Faecal: Pertaining to or of the nature of feces. [EU]

Family Planning: Programs or services designed to assist the family in controlling reproduction by either improving or diminishing fertility. [NIH]

Fat: Total lipids including phospholipids. [NIH]

Fatigue: The state of weariness following a period of exertion, mental or physical, characterized by a decreased capacity for work and reduced efficiency to respond to stimuli. [NIH]

Fatty Liver: The buildup of fat in liver cells. The most common cause is alcoholism. Other causes include obesity, diabetes, and pregnancy. Also called steatosis. [NIH]

Fatty Liver, Alcoholic: Fatty liver in alcoholics. It is potentially reversible and may be associated with alcoholic hepatitis or cirrhosis. [NIH]

Febrile: Pertaining to or characterized by fever. [EU]

Feces: The excrement discharged from the intestines, consisting of bacteria, cells exfoliated from the intestines, secretions, chiefly of the liver, and a small amount of food residue. [EU]

Fetus: The developing offspring from 7 to 8 weeks after conception until birth. [NIH]

Fibroblasts: Connective tissue cells which secrete an extracellular matrix rich in collagen and other macromolecules. [NIH]

Fibrosis: Any pathological condition where fibrous connective tissue invades any organ, usually as a consequence of inflammation or other injury. [NIH]

Flavivirus: A genus of Flaviviridae, also known as Group B arbovirus, containing several subgroups and species. Most are arboviruses transmitted by mosquitoes or ticks. The type species is yellow fever virus. [NIH]

Flexor: Muscles which flex a joint. [NIH]

Flow Cytometry: Technique using an instrument system for making, processing, and displaying one or more measurements on individual cells obtained from a cell suspension. Cells are usually stained with one or more fluorescent dyes specific to cell components of interest, e.g., DNA, and fluorescence of each cell is measured as it rapidly transverses the excitation beam (laser or mercury arc lamp). Fluorescence provides a quantitative measure of various biochemical and biophysical properties of the cell, as well as a basis for cell sorting. Other measurable optical parameters include light absorption and light scattering, the latter being applicable to the measurement of cell size, shape, density, granularity, and stain uptake. [NIH]

Fluorescence: The property of emitting radiation while being irradiated. The radiation emitted is usually of longer wavelength than that incident or absorbed, e.g., a substance can be irradiated with invisible radiation and emit visible light. X-ray fluorescence is used in diagnosis. [NIH]

Fluorescent Dyes: Dyes that emit light when exposed to light. The wave length of the emitted light is usually longer than that of the incident light. Fluorochromes are substances that cause fluorescence in other substances, i.e., dyes used to mark or label other compounds with fluorescent tags. They are used as markers in biochemistry and immunology. [NIH]

Fold: A plication or doubling of various parts of the body. [NIH]

Free Radicals: Highly reactive molecules with an unsatisfied electron valence pair. Free radicals are produced in both normal and pathological processes. They are proven or suspected agents of tissue damage in a wide variety of circumstances including radiation, damage from environment chemicals, and aging. Natural and pharmacological prevention of free radical damage is being actively investigated. [NIH]

Fulminant Hepatic Failure: Liver failure that occurs suddenly in a previously healthy person. The most common causes of FHF are acute hepatitis, acetaminophen overdose, and liver damage from prescription drugs. [NIH]

Fungi: A kingdom of eukaryotic, heterotrophic organisms that live as saprobes or parasites, including mushrooms, yeasts, smuts, molds, etc. They reproduce either sexually or asexually, and have life cycles that range from simple to complex. Filamentous fungi refer to those that grow as multicelluar colonies (mushrooms and molds). [NIH]

Fungus: A general term used to denote a group of eukaryotic protists, including mushrooms, yeasts, rusts, moulds, smuts, etc., which are characterized by the absence of chlorophyll and by the presence of a rigid cell wall composed of chitin, mannans, and sometimes cellulose. They are usually of simple morphological form or show some reversible cellular specialization, such as the formation of pseudoparenchymatous tissue in the fruiting body of a mushroom. The dimorphic fungi grow, according to environmental conditions, as moulds or yeasts. [EU]

Galactosides: Glycosides formed by the reaction of the hydroxyl group on the anomeric

carbon atom of galactose with an alcohol to form an acetal. They include both alpha- and beta-galactosides. [NIH]

Gallbladder: The pear-shaped organ that sits below the liver. Bile is concentrated and stored in the gallbladder. [NIH]

Gamma Rays: Very powerful and penetrating, high-energy electromagnetic radiation of shorter wavelength than that of x-rays. They are emitted by a decaying nucleus, usually between 0.01 and 10 MeV. They are also called nuclear x-rays. [NIH]

Gas: Air that comes from normal breakdown of food. The gases are passed out of the body through the rectum (flatus) or the mouth (burp). [NIH]

Gastric: Having to do with the stomach. [NIH]

Gastric Mucosa: Surface epithelium in the stomach that invaginates into the lamina propria, forming gastric pits. Tubular glands, characteristic of each region of the stomach (cardiac, gastric, and pyloric), empty into the gastric pits. The gastric mucosa is made up of several different kinds of cells. [NIH]

Gastrin: A hormone released after eating. Gastrin causes the stomach to produce more acid. [NIH]

Gastroenterology: A subspecialty of internal medicine concerned with the study of the physiology and diseases of the digestive system and related structures (esophagus, liver, gallbladder, and pancreas). [NIH]

Gastrointestinal: Refers to the stomach and intestines. [NIH]

Gastrointestinal tract: The stomach and intestines. [NIH]

Gelatin: A product formed from skin, white connective tissue, or bone collagen. It is used as a protein food adjuvant, plasma substitute, hemostatic, suspending agent in pharmaceutical preparations, and in the manufacturing of capsules and suppositories. [NIH]

Gene: The functional and physical unit of heredity passed from parent to offspring. Genes are pieces of DNA, and most genes contain the information for making a specific protein. [NIH]

Gene Expression: The phenotypic manifestation of a gene or genes by the processes of gene action. [NIH]

Gene Therapy: The introduction of new genes into cells for the purpose of treating disease by restoring or adding gene expression. Techniques include insertion of retroviral vectors, transfection, homologous recombination, and injection of new genes into the nuclei of single cell embryos. The entire gene therapy process may consist of multiple steps. The new genes may be introduced into proliferating cells in vivo (e.g., bone marrow) or in vitro (e.g., fibroblast cultures) and the modified cells transferred to the site where the gene expression is required. Gene therapy may be particularly useful for treating enzyme deficiency diseases, hemoglobinopathies, and leukemias and may also prove useful in restoring drug sensitivity, particularly for leukemia. [NIH]

General practitioner: A medical practitioner who does not specialize in a particular branch of medicine or limit his practice to a specific class of diseases. [NIH]

Genetic Code: The specifications for how information, stored in nucleic acid sequence (base sequence), is translated into protein sequence (amino acid sequence). The start, stop, and order of amino acids of a protein is specified by consecutive triplets of nucleotides called codons (codon). [NIH]

Genetic Engineering: Directed modification of the gene complement of a living organism by such techniques as altering the DNA, substituting genetic material by means of a virus, transplanting whole nuclei, transplanting cell hybrids, etc. [NIH]

Genetic testing: Analyzing DNA to look for a genetic alteration that may indicate an increased risk for developing a specific disease or disorder. [NIH]

Genetic transcription: The process by which the genetic information encoded in the gene, represented as a linear sequence of deoxyribonucleotides, is copied into an exactly complementary sequence of ribonucleotides known as messenger RNA. [NIH]

Genetics: The biological science that deals with the phenomena and mechanisms of heredity. [NIH]

Genital: Pertaining to the genitalia. [EU]

Genomics: The systematic study of the complete DNA sequences (genome) of organisms. [NIH]

Genotype: The genetic constitution of the individual; the characterization of the genes. [NIH]

Gestation: The period of development of the young in viviparous animals, from the time of fertilization of the ovum until birth. [EU]

Gland: An organ that produces and releases one or more substances for use in the body. Some glands produce fluids that affect tissues or organs. Others produce hormones or participate in blood production. [NIH]

Glomerular: Pertaining to or of the nature of a glomerulus, especially a renal glomerulus. [EU]

Glomeruli: Plural of glomerulus. [NIH]

Glomerulonephritis: Glomerular disease characterized by an inflammatory reaction, with leukocyte infiltration and cellular proliferation of the glomeruli, or that appears to be the result of immune glomerular injury. [NIH]

Glucose: D-Glucose. A primary source of energy for living organisms. It is naturally occurring and is found in fruits and other parts of plants in its free state. It is used therapeutically in fluid and nutrient replacement. [NIH]

Glucose Intolerance: A pathological state in which the fasting plasma glucose level is less than 140 mg per deciliter and the 30-, 60-, or 90-minute plasma glucose concentration following a glucose tolerance test exceeds 200 mg per deciliter. This condition is seen frequently in diabetes mellitus but also occurs with other diseases. [NIH]

Glutathione Peroxidase: An enzyme catalyzing the oxidation of 2 moles of glutathione in the presence of hydrogen peroxide to yield oxidized glutathione and water. EC 1.11.1.9. [NIH]

Glycine: A non-essential amino acid. It is found primarily in gelatin and silk fibroin and used therapeutically as a nutrient. It is also a fast inhibitory neurotransmitter. [NIH]

Glycoprotein: A protein that has sugar molecules attached to it. [NIH]

Glycosaminoglycans: Heteropolysaccharides which contain an N-acetylated hexosamine in a characteristic repeating disaccharide unit. The repeating structure of each disaccharide involves alternate 1,4- and 1,3-linkages consisting of either N-acetylglucosamine or N-acetylgalactosamine. [NIH]

Glycosylation: The chemical or biochemical addition of carbohydrate or glycosyl groups to other chemicals, especially peptides or proteins. Glycosyl transferases are used in this biochemical reaction. [NIH]

Gonadal: Pertaining to a gonad. [EU]

Governing Board: The group in which legal authority is vested for the control of health-related institutions and organizations. [NIH]

Graft: Healthy skin, bone, or other tissue taken from one part of the body and used to

replace diseased or injured tissue removed from another part of the body. [NIH]

Graft Rejection: An immune response with both cellular and humoral components, directed against an allogeneic transplant, whose tissue antigens are not compatible with those of the recipient. [NIH]

Gram-negative: Losing the stain or decolorized by alcohol in Gram's method of staining, a primary characteristic of bacteria having a cell wall composed of a thin layer of peptidoglycan covered by an outer membrane of lipoprotein and lipopolysaccharide. [EU]

Granule: A small pill made from sucrose. [EU]

Granulomas: Small lumps in tissues caused by inflammation. [NIH]

Growth factors: Substances made by the body that function to regulate cell division and cell survival. Some growth factors are also produced in the laboratory and used in biological therapy. [NIH]

Guanine: One of the four DNA bases. [NIH]

Habitual: Of the nature of a habit; according to habit; established by or repeated by force of habit, customary. [EU]

Haematuria: Blood in the urine. [EU]

Haemodialysis: The removal of certain elements from the blood by virtue of the difference in the rates of their diffusion through a semipermeable membrane, e.g., by means of a haemodialyzer. [EU]

Haemolysis: Disruption of the integrity of the red cell membrane causing release of haemoglobin. Haemolysis may be caused by bacterial haemolysins, by antibodies that cause complement-dependent lysis, by placing red cells in a hyptonic solution, or by defects in the red cell membrane. [EU]

Haemophilia: A haemorrhagic diathesis occurring in two main forms: 1. Haemophilia A (classic haemophilia, factor VIII deficiency), an X-linked disorder due to deficiency of coagulation factor VIII; 2. Haemophilia B (factor IX deficiency, Christmas disease), also X-linked, due to deficiency of coagulation factor IX. Both forms are determined by a mutant gene near the telomere of the long arm of the X chromosome (Xq), but a different loci, and are characterized by subcutaneous and intramuscular haemorrhages; bleeding from the mouth, gums, lips, and tongue; haematuria; and haemarthroses. [EU]

Haemorrhage: The escape of blood from the vessels; bleeding. Small haemorrhages are classified according to size as petechiae (very small), purpura (up to 1 cm), and ecchymoses (larger). The massive accumulation of blood within a tissue is called a haematoma. [EU]

Half-Life: The time it takes for a substance (drug, radioactive nuclide, or other) to lose half of its pharmacologic, physiologic, or radiologic activity. [NIH]

Haploid: An organism with one basic chromosome set, symbolized by n; the normal condition of gametes in diploids. [NIH]

Haptens: Small antigenic determinants capable of eliciting an immune response only when coupled to a carrier. Haptens bind to antibodies but by themselves cannot elicit an antibody response. [NIH]

Headache: Pain in the cranial region that may occur as an isolated and benign symptom or as a manifestation of a wide variety of conditions including subarachnoid hemorrhage; craniocerebral trauma; central nervous system infections; intracranial hypertension; and other disorders. In general, recurrent headaches that are not associated with a primary disease process are referred to as headache disorders (e.g., migraine). [NIH]

Health Services: Services for the diagnosis and treatment of disease and the maintenance of

health. [NIH]

Health Status: The level of health of the individual, group, or population as subjectively assessed by the individual or by more objective measures. [NIH]

Heart attack: A seizure of weak or abnormal functioning of the heart. [NIH]

Hematocrit: Measurement of the volume of packed red cells in a blood specimen by centrifugation. The procedure is performed using a tube with graduated markings or with automated blood cell counters. It is used as an indicator of erythrocyte status in disease. For example, anemia shows a low hematocrit, polycythemia, high values. [NIH]

Hematology: A subspecialty of internal medicine concerned with morphology, physiology, and pathology of the blood and blood-forming tissues. [NIH]

Heme: The color-furnishing portion of hemoglobin. It is found free in tissues and as the prosthetic group in many hemeproteins. [NIH]

Hemodialysis: The use of a machine to clean wastes from the blood after the kidneys have failed. The blood travels through tubes to a dialyzer, which removes wastes and extra fluid. The cleaned blood then flows through another set of tubes back into the body. [NIH]

Hemoglobin: One of the fractions of glycosylated hemoglobin A1c. Glycosylated hemoglobin is formed when linkages of glucose and related monosaccharides bind to hemoglobin A and its concentration represents the average blood glucose level over the previous several weeks. HbA1c levels are used as a measure of long-term control of plasma glucose (normal, 4 to 6 percent). In controlled diabetes mellitus, the concentration of glycosylated hemoglobin A is within the normal range, but in uncontrolled cases the level may be 3 to 4 times the normal conentration. Generally, complications are substantially lower among patients with Hb levels of 7 percent or less than in patients with HbA1c levels of 9 percent or more. [NIH]

Hemoglobinopathies: A group of inherited disorders characterized by structural alterations within the hemoglobin molecule. [NIH]

Hemoglobinuria: The presence of free hemoglobin in the urine. [NIH]

Hemolysis: The destruction of erythrocytes by many different causal agents such as antibodies, bacteria, chemicals, temperature, and changes in tonicity. [NIH]

Hemolytic: A disease that affects the blood and blood vessels. It destroys red blood cells, cells that cause the blood to clot, and the lining of blood vessels. HUS is often caused by the Escherichia coli bacterium in contaminated food. People with HUS may develop acute renal failure. [NIH]

Hemophilia: Refers to a group of hereditary disorders in which affected individuals fail to make enough of certain proteins needed to form blood clots. [NIH]

Hemorrhage: Bleeding or escape of blood from a vessel. [NIH]

Hepatic: Refers to the liver. [NIH]

Hepatic Artery: A branch of the celiac artery that distributes to the stomach, pancreas, duodenum, liver, gallbladder, and greater omentum. [NIH]

Hepatic Encephalopathy: A condition that may cause loss of consciousness and coma. It is usually the result of advanced liver disease. Also called hepatic coma. [NIH]

Hepatitis: Inflammation of the liver and liver disease involving degenerative or necrotic alterations of hepatocytes. [NIH]

Hepatitis A: Hepatitis caused by hepatovirus. It can be transmitted through fecal contamination of food or water. [NIH]

Hepatitis B: Hepatitis caused by hepatitis B virus. It may be transmitted by transfusion of

contaminated blood or blood products. [NIH]

Hepatitis C: A form of hepatitis, similar to type B post-transfusion hepatitis, but caused by a virus which is serologically distinct from the agents of hepatitis A, B, and E, and which may persist in the blood of chronic asymptomatic carriers. Hepatitis C is parenterally transmitted and associated with transfusions and drug abuse. [NIH]

Hepatitis D: Hepatitis caused by the hepatitis delta virus in association with hepatitis B. It is endemic in some European countries and is seen in drug users, hemophiliacs, and polytransfused persons. [NIH]

Hepatitis Delta Virus: A defective virus, containing particles of RNA nucleoprotein in virion-like form, present in patients with acute hepatitis B and chronic hepatitis. Officially this is classified as a subviral satellite RNA. [NIH]

Hepatitis Viruses: Any of the viruses that cause inflammation of the liver. They include both DNA and RNA viruses as well viruses from humans and animals. [NIH]

Hepatitis, Alcoholic: An acute or chronic degenerative and inflammatory lesion of the liver in the alcoholic which is potentially progressive though sometimes reversible. It does not necessarily include steatosis, fibrosis, or cirrhosis of alcoholics, although it is frequently associated with these conditions. It is characterized by liver cell necrosis, infiltration by polymorphonuclear leukocytes and lymphocytes, and Mallory bodies. The morphologic changes of chronic alcoholic hepatitis are not likely to be confused with chronic hepatitis. [NIH]

Hepatitis, Chronic: A collective term for a clinical and pathological syndrome which has several causes and is characterized by varying degrees of hepatocellular necrosis and inflammation. Specific forms of chronic hepatitis include autoimmune hepatitis, chronic hepatitis B, chronic hepatitis C, chronic hepatitis D, indeterminate chronic viral hepatitis, cryptogenic chronic hepatitis, and drug-related chronic hepatitis. [NIH]

Hepatobiliary: Pertaining to the liver and the bile or the biliary ducts. [EU]

Hepatoblastoma: A type of liver tumor that occurs in infants and children. [NIH]

Hepatocellular: Pertaining to or affecting liver cells. [EU]

Hepatocellular carcinoma: A type of adenocarcinoma, the most common type of liver tumor. [NIH]

Hepatocyte: A liver cell. [NIH]

Hepatocyte Growth Factor: Multifunctional growth factor which regulates both cell growth and cell motility. It exerts a strong mitogenic effect on hepatocytes and primary epithelial cells. Its receptor is proto-oncogene protein C-met. [NIH]

Hepatologist: A doctor who specializes in liver diseases. [NIH]

Hepatology: The field of medicine concerned with the functions and disorders of the liver. [NIH]

Hepatoma: A liver tumor. [NIH]

Hepatotoxic: Toxic to liver cells. [EU]

Hepatotoxicity: How much damage a medicine or other substance does to the liver. [NIH]

Hepatovirus: A genus of Picornaviridae causing infectious hepatitis naturally in humans and experimentally in other primates. It is transmitted through fecal contamination of food or water. [NIH]

Hereditary: Of, relating to, or denoting factors that can be transmitted genetically from one generation to another. [NIH]

Heredity: 1. The genetic transmission of a particular quality or trait from parent to offspring.

2. The genetic constitution of an individual. [EU]

Herpes: Any inflammatory skin disease caused by a herpesvirus and characterized by the formation of clusters of small vesicles. When used alone, the term may refer to herpes simplex or to herpes zoster. [EU]

Herpes virus: A member of the herpes family of viruses. [NIH]

Herpes Zoster: Acute vesicular inflammation. [NIH]

Heterogeneity: The property of one or more samples or populations which implies that they are not identical in respect of some or all of their parameters, e. g. heterogeneity of variance. [NIH]

Histidine: An essential amino acid important in a number of metabolic processes. It is required for the production of histamine. [NIH]

Histology: The study of tissues and cells under a microscope. [NIH]

Hog Cholera: An acute, highly contagious disease affecting swine of all ages and caused by the hog cholera virus. It has a sudden onset with high morbidity and mortality. [NIH]

Hog Cholera Virus: A species of the Pestivirus genus causing exceedingly contagious and fatal hemorrhagic disease of swine. [NIH]

Homeostasis: The processes whereby the internal environment of an organism tends to remain balanced and stable. [NIH]

Homogeneous: Consisting of or composed of similar elements or ingredients; of a uniform quality throughout. [EU]

Homologous: Corresponding in structure, position, origin, etc., as (a) the feathers of a bird and the scales of a fish, (b) antigen and its specific antibody, (c) allelic chromosomes. [EU]

Hormonal: Pertaining to or of the nature of a hormone. [EU]

Hormone: A substance in the body that regulates certain organs. Hormones such as gastrin help in breaking down food. Some hormones come from cells in the stomach and small intestine. [NIH]

Horseradish Peroxidase: An enzyme isolated from horseradish which is able to act as an antigen. It is frequently used as a histochemical tracer for light and electron microscopy. Its antigenicity has permitted its use as a combined antigen and marker in experimental immunology. [NIH]

Humoral: Of, relating to, proceeding from, or involving a bodily humour - now often used of endocrine factors as opposed to neural or somatic. [EU]

Humour: 1. A normal functioning fluid or semifluid of the body (as the blood, lymph or bile) especially of vertebrates. 2. A secretion that is itself an excitant of activity (as certain hormones). [EU]

Hybrid: Cross fertilization between two varieties or, more usually, two species of vines, see also crossing. [NIH]

Hybridoma: A hybrid cell resulting from the fusion of a specific antibody-producing spleen cell with a myeloma cell. [NIH]

Hydrogen: The first chemical element in the periodic table. It has the atomic symbol H, atomic number 1, and atomic weight 1. It exists, under normal conditions, as a colorless, odorless, tasteless, diatomic gas. Hydrogen ions are protons. Besides the common H1 isotope, hydrogen exists as the stable isotope deuterium and the unstable, radioactive isotope tritium. [NIH]

Hydrogen Peroxide: A strong oxidizing agent used in aqueous solution as a ripening agent,

bleach, and topical anti-infective. It is relatively unstable and solutions deteriorate over time unless stabilized by the addition of acetanilide or similar organic materials. [NIH]

Hydrolysis: The process of cleaving a chemical compound by the addition of a molecule of water. [NIH]

Hydrophobic: Not readily absorbing water, or being adversely affected by water, as a hydrophobic colloid. [EU]

Hydroxyproline: A hydroxylated form of the imino acid proline. A deficiency in ascorbic acid can result in impaired hydroxyproline formation. [NIH]

Hyperbilirubinemia: Pathologic process consisting of an abnormal increase in the amount of bilirubin in the circulating blood, which may result in jaundice. [NIH]

Hypercholesterolemia: Abnormally high levels of cholesterol in the blood. [NIH]

Hyperlipidemia: An excess of lipids in the blood. [NIH]

Hyperplasia: An increase in the number of cells in a tissue or organ, not due to tumor formation. It differs from hypertrophy, which is an increase in bulk without an increase in the number of cells. [NIH]

Hyperreflexia: Exaggeration of reflexes. [EU]

Hypersensitivity: Altered reactivity to an antigen, which can result in pathologic reactions upon subsequent exposure to that particular antigen. [NIH]

Hypertension: Persistently high arterial blood pressure. Currently accepted threshold levels are 140 mm Hg systolic and 90 mm Hg diastolic pressure. [NIH]

Hyperthermia: A type of treatment in which body tissue is exposed to high temperatures to damage and kill cancer cells or to make cancer cells more sensitive to the effects of radiation and certain anticancer drugs. [NIH]

Hypertriglyceridemia: Condition of elevated triglyceride concentration in the blood; an inherited form occurs in familial hyperlipoproteinemia IIb and hyperlipoproteinemia type IV. It has been linked to higher risk of heart disease and arteriosclerosis. [NIH]

Hysterotomy: An incision in the uterus, performed through either the abdomen or the vagina. [NIH]

Idiopathic: Describes a disease of unknown cause. [NIH]

Immune function: Production and action of cells that fight disease or infection. [NIH]

Immune response: The activity of the immune system against foreign substances (antigens). [NIH]

Immune Sera: Serum that contains antibodies. It is obtained from an animal that has been immunized either by antigen injection or infection with microorganisms containing the antigen. [NIH]

Immune system: The organs, cells, and molecules responsible for the recognition and disposal of foreign ("non-self") material which enters the body. [NIH]

Immunization: Deliberate stimulation of the host's immune response. Active immunization involves administration of antigens or immunologic adjuvants. Passive immunization involves administration of immune sera or lymphocytes or their extracts (e.g., transfer factor, immune RNA) or transplantation of immunocompetent cell producing tissue (thymus or bone marrow). [NIH]

Immunoassay: Immunochemical assay or detection of a substance by serologic or immunologic methods. Usually the substance being studied serves as antigen both in antibody production and in measurement of antibody by the test substance. [NIH]

Immunochemistry: Field of chemistry that pertains to immunological phenomena and the study of chemical reactions related to antigen stimulation of tissues. It includes physicochemical interactions between antigens and antibodies. [NIH]

Immunocompromised: Having a weakened immune system caused by certain diseases or treatments. [NIH]

Immunocompromised Host: A human or animal whose immunologic mechanism is deficient because of an immunodeficiency disorder or other disease or as the result of the administration of immunosuppressive drugs or radiation. [NIH]

Immunodeficiency: The decreased ability of the body to fight infection and disease. [NIH]

Immunodominant Epitopes: Subunits of the antigenic determinant that are most easily recognized by the immune system and thus most influence the specificity of the induced antibody. [NIH]

Immunogenic: Producing immunity; evoking an immune response. [EU]

Immunoglobulin: A protein that acts as an antibody. [NIH]

Immunologic: The ability of the antibody-forming system to recall a previous experience with an antigen and to respond to a second exposure with the prompt production of large amounts of antibody. [NIH]

Immunology: The study of the body's immune system. [NIH]

Immunosuppression: Deliberate prevention or diminution of the host's immune response. It may be nonspecific as in the administration of immunosuppressive agents (drugs or radiation) or by lymphocyte depletion or may be specific as in desensitization or the simultaneous administration of antigen and immunosuppressive drugs. [NIH]

Immunosuppressive: Describes the ability to lower immune system responses. [NIH]

Immunosuppressive Agents: Agents that suppress immune function by one of several mechanisms of action. Classical cytotoxic immunosuppressants act by inhibiting DNA synthesis. Others may act through activation of suppressor T-cell populations or by inhibiting the activation of helper cells. While immunosuppression has been brought about in the past primarily to prevent rejection of transplanted organs, new applications involving mediation of the effects of interleukins and other cytokines are emerging. [NIH]

Immunosuppressive therapy: Therapy used to decrease the body's immune response, such as drugs given to prevent transplant rejection. [NIH]

Immunotherapy: Manipulation of the host's immune system in treatment of disease. It includes both active and passive immunization as well as immunosuppressive therapy to prevent graft rejection. [NIH]

Impairment: In the context of health experience, an impairment is any loss or abnormality of psychological, physiological, or anatomical structure or function. [NIH]

In situ: In the natural or normal place; confined to the site of origin without invasion of neighbouring tissues. [EU]

In Situ Hybridization: A technique that localizes specific nucleic acid sequences within intact chromosomes, eukaryotic cells, or bacterial cells through the use of specific nucleic acid-labeled probes. [NIH]

In vitro: In the laboratory (outside the body). The opposite of in vivo (in the body). [NIH]

In vivo: In the body. The opposite of in vitro (outside the body or in the laboratory). [NIH]

Incision: A cut made in the body during surgery. [NIH]

Incubation: The development of an infectious disease from the entrance of the pathogen to

the appearance of clinical symptoms. [EU]

Incubation period: The period of time likely to elapse between exposure to the agent of the disease and the onset of clinical symptoms. [NIH]

Indolent: A type of cancer that grows slowly. [NIH]

Induction: The act or process of inducing or causing to occur, especially the production of a specific morphogenetic effect in the developing embryo through the influence of evocators or organizers, or the production of anaesthesia or unconsciousness by use of appropriate agents. [EU]

Infancy: The period of complete dependency prior to the acquisition of competence in walking, talking, and self-feeding. [NIH]

Infarction: A pathological process consisting of a sudden insufficient blood supply to an area, which results in necrosis of that area. It is usually caused by a thrombus, an embolus, or a vascular torsion. [NIH]

Infection: 1. Invasion and multiplication of microorganisms in body tissues, which may be clinically unapparent or result in local cellular injury due to competitive metabolism, toxins, intracellular replication, or antigen-antibody response. The infection may remain localized, subclinical, and temporary if the body's defensive mechanisms are effective. A local infection may persist and spread by extension to become an acute, subacute, or chronic clinical infection or disease state. A local infection may also become systemic when the microorganisms gain access to the lymphatic or vascular system. 2. An infectious disease. [EU]

Infection Control: Programs of disease surveillance, generally within health care facilities, designed to investigate, prevent, and control the spread of infections and their causative microorganisms. [NIH]

Infiltration: The diffusion or accumulation in a tissue or cells of substances not normal to it or in amounts of the normal. Also, the material so accumulated. [EU]

Inflammation: A pathological process characterized by injury or destruction of tissues caused by a variety of cytologic and chemical reactions. It is usually manifested by typical signs of pain, heat, redness, swelling, and loss of function. [NIH]

Influenza: An acute viral infection involving the respiratory tract. It is marked by inflammation of the nasal mucosa, the pharynx, and conjunctiva, and by headache and severe, often generalized, myalgia. [NIH]

Infusion: A method of putting fluids, including drugs, into the bloodstream. Also called intravenous infusion. [NIH]

Ingestion: Taking into the body by mouth [NIH]

Inhalation: The drawing of air or other substances into the lungs. [EU]

Initiation: Mutation induced by a chemical reactive substance causing cell changes; being a step in a carcinogenic process. [NIH]

Initiator: A chemically reactive substance which may cause cell changes if ingested, inhaled or absorbed into the body; the substance may thus initiate a carcinogenic process. [NIH]

Inorganic: Pertaining to substances not of organic origin. [EU]

Insight: The capacity to understand one's own motives, to be aware of one's own psychodynamics, to appreciate the meaning of symbolic behavior. [NIH]

Insulator: Material covering the metal conductor of the lead. It is usually polyurethane or silicone. [NIH]

Insulin: A protein hormone secreted by beta cells of the pancreas. Insulin plays a major role

in the regulation of glucose metabolism, generally promoting the cellular utilization of glucose. It is also an important regulator of protein and lipid metabolism. Insulin is used as a drug to control insulin-dependent diabetes mellitus. [NIH]

Insulin-dependent diabetes mellitus: A disease characterized by high levels of blood glucose resulting from defects in insulin secretion, insulin action, or both. Autoimmune, genetic, and environmental factors are involved in the development of type I diabetes. [NIH]

Interferon: A biological response modifier (a substance that can improve the body's natural response to disease). Interferons interfere with the division of cancer cells and can slow tumor growth. There are several types of interferons, including interferon-alpha, -beta, and -gamma. These substances are normally produced by the body. They are also made in the laboratory for use in treating cancer and other diseases. [NIH]

Interferon Alfa-2b: A recombinant alfa interferon consisting of 165 amino acid residues with arginine in position 23 and histidine in position 34. It is used extensively as an antiviral and antineoplastic agent. [NIH]

Interferon-alpha: One of the type I interferons produced by peripheral blood leukocytes or lymphoblastoid cells when exposed to live or inactivated virus, double-stranded RNA, or bacterial products. It is the major interferon produced by virus-induced leukocyte cultures and, in addition to its pronounced antiviral activity, it causes activation of NK cells. [NIH]

Interferon-beta: One of the type I interferons produced by fibroblasts in response to stimulation by live or inactivated virus or by double-stranded RNA. It is a cytokine with antiviral, antiproliferative, and immunomodulating activity. [NIH]

Interleukin-1: A soluble factor produced by monocytes, macrophages, and other cells which activates T-lymphocytes and potentiates their response to mitogens or antigens. IL-1 consists of two distinct forms, IL-1 alpha and IL-1 beta which perform the same functions but are distinct proteins. The biological effects of IL-1 include the ability to replace macrophage requirements for T-cell activation. The factor is distinct from interleukin-2. [NIH]

Interleukin-10: Factor that is a coregulator of mast cell growth. It is produced by T-cells and B-cells and shows extensive homology with the Epstein-Barr virus BCRFI gene. [NIH]

Interleukin-2: Chemical mediator produced by activated T lymphocytes and which regulates the proliferation of T cells, as well as playing a role in the regulation of NK cell activity. [NIH]

Interleukin-8: A cytokine that activates neutrophils and attracts neutrophils and T-lymphocytes. It is released by several cell types including monocytes, macrophages, T-lymphocytes, fibroblasts, endothelial cells, and keratinocytes by an inflammatory stimulus. IL-8 is a member of the beta-thromboglobulin superfamily and structurally related to platelet factor 4. [NIH]

Intermittent: Occurring at separated intervals; having periods of cessation of activity. [EU]

Interstitial: Pertaining to or situated between parts or in the interspaces of a tissue. [EU]

Intestinal: Having to do with the intestines. [NIH]

Intestines: The section of the alimentary canal from the stomach to the anus. It includes the large intestine and small intestine. [NIH]

Intoxication: Poisoning, the state of being poisoned. [EU]

Intracellular: Inside a cell. [NIH]

Intracellular Membranes: Membranes of subcellular structures. [NIH]

Intrahepatic: Within the liver. [NIH]

Intramuscular: IM. Within or into muscle. [NIH]

Intraperitoneal: IP. Within the peritoneal cavity (the area that contains the abdominal organs). [NIH]

Intravenous: IV. Into a vein. [NIH]

Intrinsic: Situated entirely within or pertaining exclusively to a part. [EU]

Intubation: Introduction of a tube into a hollow organ to restore or maintain patency if obstructed. It is differentiated from catheterization in that the insertion of a catheter is usually performed for the introducing or withdrawing of fluids from the body. [NIH]

Invasive: 1. Having the quality of invasiveness. 2. Involving puncture or incision of the skin or insertion of an instrument or foreign material into the body; said of diagnostic techniques. [EU]

Invertebrates: Animals that have no spinal column. [NIH]

Involuntary: Reaction occurring without intention or volition. [NIH]

Ionizing: Radiation comprising charged particles, e. g. electrons, protons, alpha-particles, etc., having sufficient kinetic energy to produce ionization by collision. [NIH]

Ions: An atom or group of atoms that have a positive or negative electric charge due to a gain (negative charge) or loss (positive charge) of one or more electrons. Atoms with a positive charge are known as cations; those with a negative charge are anions. [NIH]

Jaundice: A clinical manifestation of hyperbilirubinemia, consisting of deposition of bile pigments in the skin, resulting in a yellowish staining of the skin and mucous membranes. [NIH]

Kb: A measure of the length of DNA fragments, 1 Kb = 1000 base pairs. The largest DNA fragments are up to 50 kilobases long. [NIH]

Keratinocytes: Epidermal cells which synthesize keratin and undergo characteristic changes as they move upward from the basal layers of the epidermis to the cornified (horny) layer of the skin. Successive stages of differentiation of the keratinocytes forming the epidermal layers are basal cell, spinous or prickle cell, and the granular cell. [NIH]

Keto: It consists of 8 carbon atoms and within the endotoxins, it connects poysaccharide and lipid A. [NIH]

Kidney Transplantation: The transference of a kidney from one human or animal to another. [NIH]

Kinetic: Pertaining to or producing motion. [EU]

Labile: 1. Gliding; moving from point to point over the surface; unstable; fluctuating. 2. Chemically unstable. [EU]

Laceration: 1. The act of tearing. 2. A torn, ragged, mangled wound. [EU]

Large Intestine: The part of the intestine that goes from the cecum to the rectum. The large intestine absorbs water from stool and changes it from a liquid to a solid form. The large intestine is 5 feet long and includes the appendix, cecum, colon, and rectum. Also called colon. [NIH]

Latent: Phoria which occurs at one distance or another and which usually has no troublesome effect. [NIH]

Lavage: A cleaning of the stomach and colon. Uses a special drink and enemas. [NIH]

Least-Squares Analysis: A principle of estimation in which the estimates of a set of parameters in a statistical model are those quantities minimizing the sum of squared differences between the observed values of a dependent variable and the values predicted by the model. [NIH]

Lectin: A complex molecule that has both protein and sugars. Lectins are able to bind to the outside of a cell and cause biochemical changes in it. Lectins are made by both animals and plants. [NIH]

Lesion: An area of abnormal tissue change. [NIH]

Leukapheresis: The preparation of leukocyte concentrates with the return of red cells and leukocyte-poor plasma to the donor. [NIH]

Leukemia: Cancer of blood-forming tissue. [NIH]

Leukocytes: White blood cells. These include granular leukocytes (basophils, eosinophils, and neutrophils) as well as non-granular leukocytes (lymphocytes and monocytes). [NIH]

Leukoencephalopathy: A condition with spongy holes in the brain's white matter. [NIH]

Lichen Planus: An inflammatory, pruritic disease of the skin and mucous membranes, which can be either generalized or localized. It is characterized by distinctive purplish, flat-topped papules having a predilection for the trunk and flexor surfaces. The lesions may be discrete or coalesce to form plaques. Histologically, there is a "saw-tooth" pattern of epidermal hyperplasia and vacuolar alteration of the basal layer of the epidermis along with an intense upper dermal inflammatory infiltrate composed predominantly of T-cells. Etiology is unknown. [NIH]

Life cycle: The successive stages through which an organism passes from fertilized ovum or spore to the fertilized ovum or spore of the next generation. [NIH]

Life Expectancy: A figure representing the number of years, based on known statistics, to which any person of a given age may reasonably expect to live. [NIH]

Ligaments: Shiny, flexible bands of fibrous tissue connecting together articular extremities of bones. They are pliant, tough, and inextensile. [NIH]

Ligands: A RNA simulation method developed by the MIT. [NIH]

Likelihood Functions: Functions constructed from a statistical model and a set of observed data which give the probability of that data for various values of the unknown model parameters. Those parameter values that maximize the probability are the maximum likelihood estimates of the parameters. [NIH]

Linear Models: Statistical models in which the value of a parameter for a given value of a factor is assumed to be equal to a + bx, where a and b are constants. The models predict a linear regression. [NIH]

Linkage: The tendency of two or more genes in the same chromosome to remain together from one generation to the next more frequently than expected according to the law of independent assortment. [NIH]

Lip: Either of the two fleshy, full-blooded margins of the mouth. [NIH]

Lipid: Fat. [NIH]

Lipid Peroxidation: Peroxidase catalyzed oxidation of lipids using hydrogen peroxide as an electron acceptor. [NIH]

Lipid Peroxides: Peroxides produced in the presence of a free radical by the oxidation of unsaturated fatty acids in the cell in the presence of molecular oxygen. The formation of lipid peroxides results in the destruction of the original lipid leading to the loss of integrity of the membranes. They therefore cause a variety of toxic effects in vivo and their formation is considered a pathological process in biological systems. Their formation can be inhibited by antioxidants, such as vitamin E, structural separation or low oxygen tension. [NIH]

Lipopolysaccharide: Substance consisting of polysaccaride and lipid. [NIH]

Lipoprotein: Any of the lipid-protein complexes in which lipids are transported in the

blood; lipoprotein particles consist of a spherical hydrophobic core of triglycerides or cholesterol esters surrounded by an amphipathic monolayer of phospholipids, cholesterol, and apolipoproteins; the four principal classes are high-density, low-density, and very-low-density lipoproteins and chylomicrons. [EU]

Liver: A large, glandular organ located in the upper abdomen. The liver cleanses the blood and aids in digestion by secreting bile. [NIH]

Liver cancer: A disease in which malignant (cancer) cells are found in the tissues of the liver. [NIH]

Liver Cirrhosis: Liver disease in which the normal microcirculation, the gross vascular anatomy, and the hepatic architecture have been variably destroyed and altered with fibrous septa surrounding regenerated or regenerating parenchymal nodules. [NIH]

Liver Transplantation: The transference of a part of or an entire liver from one human or animal to another. [NIH]

Localization: The process of determining or marking the location or site of a lesion or disease. May also refer to the process of keeping a lesion or disease in a specific location or site. [NIH]

Localized: Cancer which has not metastasized yet. [NIH]

Locomotion: Movement or the ability to move from one place or another. It can refer to humans, vertebrate or invertebrate animals, and microorganisms. [NIH]

Locoregional: The characteristic of a disease-producing organism to transfer itself, but typically to the same region of the body (a leg, the lungs, .) [EU]

Logistic Models: Statistical models which describe the relationship between a qualitative dependent variable (that is, one which can take only certain discrete values, such as the presence or absence of a disease) and an independent variable. A common application is in epidemiology for estimating an individual's risk (probability of a disease) as a function of a given risk factor. [NIH]

Longitudinal Studies: Studies in which variables relating to an individual or group of individuals are assessed over a period of time. [NIH]

Longitudinal study: Also referred to as a "cohort study" or "prospective study"; the analytic method of epidemiologic study in which subsets of a defined population can be identified who are, have been, or in the future may be exposed or not exposed, or exposed in different degrees, to a factor or factors hypothesized to influence the probability of occurrence of a given disease or other outcome. The main feature of this type of study is to observe large numbers of subjects over an extended time, with comparisons of incidence rates in groups that differ in exposure levels. [NIH]

Long-Term Care: Care over an extended period, usually for a chronic condition or disability, requiring periodic, intermittent, or continuous care. [NIH]

Loop: A wire usually of platinum bent at one end into a small loop (usually 4 mm inside diameter) and used in transferring microorganisms. [NIH]

Loss of Heterozygosity: The loss of one allele at a specific locus, caused by a deletion mutation; or loss of a chromosome from a chromosome pair. It is detected when heterozygous markers for a locus appear monomorphic because one of the alleles was deleted. When this occurs at a tumor suppressor gene locus where one of the alleles is already abnormal, it can result in neoplastic transformation. [NIH]

Low-density lipoprotein: Lipoprotein that contains most of the cholesterol in the blood. LDL carries cholesterol to the tissues of the body, including the arteries. A high level of LDL increases the risk of heart disease. LDL typically contains 60 to 70 percent of the total serum

cholesterol and both are directly correlated with CHD risk. [NIH]

Luciferase: Any one of several enzymes that catalyze the bioluminescent reaction in certain marine crustaceans, fish, bacteria, and insects. The enzyme is a flavoprotein; it oxidizes luciferins to an electronically excited compound that emits energy in the form of light. The color of light emitted varies with the organism. The firefly enzyme is a valuable reagent for measurement of ATP concentration. (Dorland, 27th ed) EC 1.13.12.-. [NIH]

Luminescence: The property of giving off light without emitting a corresponding degree of heat. It includes the luminescence of inorganic matter or the bioluminescence of human matter, invertebrates and other living organisms. For the luminescence of bacteria, bacterial luminescence is available. [NIH]

Lupus: A form of cutaneous tuberculosis. It is seen predominantly in women and typically involves the nasal, buccal, and conjunctival mucosa. [NIH]

Lymph: The almost colorless fluid that travels through the lymphatic system and carries cells that help fight infection and disease. [NIH]

Lymph node: A rounded mass of lymphatic tissue that is surrounded by a capsule of connective tissue. Also known as a lymph gland. Lymph nodes are spread out along lymphatic vessels and contain many lymphocytes, which filter the lymphatic fluid (lymph). [NIH]

Lymphatic: The tissues and organs, including the bone marrow, spleen, thymus, and lymph nodes, that produce and store cells that fight infection and disease. [NIH]

Lymphatic system: The tissues and organs that produce, store, and carry white blood cells that fight infection and other diseases. This system includes the bone marrow, spleen, thymus, lymph nodes and a network of thin tubes that carry lymph and white blood cells. These tubes branch, like blood vessels, into all the tissues of the body. [NIH]

Lymphocyte: A white blood cell. Lymphocytes have a number of roles in the immune system, including the production of antibodies and other substances that fight infection and diseases. [NIH]

Lymphocyte Count: A count of the number of lymphocytes in the blood. [NIH]

Lymphocyte Depletion: Immunosuppression by reduction of circulating lymphocytes or by T-cell depletion of bone marrow. The former may be accomplished in vivo by thoracic duct drainage or administration of antilymphocyte serum. The latter is performed ex vivo on bone marrow before its transplantation. [NIH]

Lymphocytic: Referring to lymphocytes, a type of white blood cell. [NIH]

Lymphoid: Referring to lymphocytes, a type of white blood cell. Also refers to tissue in which lymphocytes develop. [NIH]

Lymphoma: A general term for various neoplastic diseases of the lymphoid tissue. [NIH]

Lymphoproliferative: Disorders characterized by proliferation of lymphoid tissue, general or unspecified. [NIH]

Lymphoproliferative Disorders: Disorders characterized by proliferation of lymphoid tissue, general or unspecified. [NIH]

Lytic: 1. Pertaining to lysis or to a lysin. 2. Producing lysis. [EU]

Macrophage: A type of white blood cell that surrounds and kills microorganisms, removes dead cells, and stimulates the action of other immune system cells. [NIH]

Magnetic Resonance Imaging: Non-invasive method of demonstrating internal anatomy based on the principle that atomic nuclei in a strong magnetic field absorb pulses of radiofrequency energy and emit them as radiowaves which can be reconstructed into

computerized images. The concept includes proton spin tomographic techniques. [NIH]

Magnetic Resonance Spectroscopy: Spectroscopic method of measuring the magnetic moment of elementary particles such as atomic nuclei, protons or electrons. It is employed in clinical applications such as NMR Tomography (magnetic resonance imaging). [NIH]

Major Histocompatibility Complex: The genetic region which contains the loci of genes which determine the structure of the serologically defined (SD) and lymphocyte-defined (LD) transplantation antigens, genes which control the structure of the immune response-associated (Ia) antigens, the immune response (Ir) genes which control the ability of an animal to respond immunologically to antigenic stimuli, and genes which determine the structure and/or level of the first four components of complement. [NIH]

Malignancy: A cancerous tumor that can invade and destroy nearby tissue and spread to other parts of the body. [NIH]

Malignant: Cancerous; a growth with a tendency to invade and destroy nearby tissue and spread to other parts of the body. [NIH]

Malignant tumor: A tumor capable of metastasizing. [NIH]

Malnutrition: A condition caused by not eating enough food or not eating a balanced diet. [NIH]

Mammary: Pertaining to the mamma, or breast. [EU]

Mediate: Indirect; accomplished by the aid of an intervening medium. [EU]

MEDLINE: An online database of MEDLARS, the computerized bibliographic Medical Literature Analysis and Retrieval System of the National Library of Medicine. [NIH]

Meiosis: A special method of cell division, occurring in maturation of the germ cells, by means of which each daughter nucleus receives half the number of chromosomes characteristic of the somatic cells of the species. [NIH]

Melanin: The substance that gives the skin its color. [NIH]

Membrane: A very thin layer of tissue that covers a surface. [NIH]

Membrane Fusion: The adherence of cell membranes, intracellular membranes, or artifical membrane models of either to each other or to viruses, parasites, or interstitial particles through a variety of chemical and physical processes. [NIH]

Memory: Complex mental function having four distinct phases: (1) memorizing or learning, (2) retention, (3) recall, and (4) recognition. Clinically, it is usually subdivided into immediate, recent, and remote memory. [NIH]

Meninges: The three membranes that cover and protect the brain and spinal cord. [NIH]

Mental: Pertaining to the mind; psychic. 2. (L. mentum chin) pertaining to the chin. [EU]

Mental Disorders: Psychiatric illness or diseases manifested by breakdowns in the adaptational process expressed primarily as abnormalities of thought, feeling, and behavior producing either distress or impairment of function. [NIH]

Mental Health: The state wherein the person is well adjusted. [NIH]

Mentors: Senior professionals who provide guidance, direction and support to those persons desirous of improvement in academic positions, administrative positions or other career development situations. [NIH]

Mercury: A silver metallic element that exists as a liquid at room temperature. It has the atomic symbol Hg (from hydrargyrum, liquid silver), atomic number 80, and atomic weight 200.59. Mercury is used in many industrial applications and its salts have been employed therapeutically as purgatives, antisyphilitics, disinfectants, and astringents. It can be

absorbed through the skin and mucous membranes which leads to mercury poisoning. Because of its toxicity, the clinical use of mercury and mercurials is diminishing. [NIH]

Metabolic disorder: A condition in which normal metabolic processes are disrupted, usually because of a missing enzyme. [NIH]

Metabolite: Any substance produced by metabolism or by a metabolic process. [EU]

Methionine: A sulfur containing essential amino acid that is important in many body functions. It is a chelating agent for heavy metals. [NIH]

MI: Myocardial infarction. Gross necrosis of the myocardium as a result of interruption of the blood supply to the area; it is almost always caused by atherosclerosis of the coronary arteries, upon which coronary thrombosis is usually superimposed. [NIH]

Microbe: An organism which cannot be observed with the naked eye; e. g. unicellular animals, lower algae, lower fungi, bacteria. [NIH]

Microbiology: The study of microorganisms such as fungi, bacteria, algae, archaea, and viruses. [NIH]

Microcirculation: The vascular network lying between the arterioles and venules; includes capillaries, metarterioles and arteriovenous anastomoses. Also, the flow of blood through this network. [NIH]

Microorganism: An organism that can be seen only through a microscope. Microorganisms include bacteria, protozoa, algae, and fungi. Although viruses are not considered living organisms, they are sometimes classified as microorganisms. [NIH]

Migration: The systematic movement of genes between populations of the same species, geographic race, or variety. [NIH]

Milliliter: A measure of volume for a liquid. A milliliter is approximately 950-times smaller than a quart and 30-times smaller than a fluid ounce. A milliliter of liquid and a cubic centimeter (cc) of liquid are the same. [NIH]

Mitochondria: Parts of a cell where aerobic production (also known as cell respiration) takes place. [NIH]

Mitochondrial Swelling: Increase in volume of mitochondria due to an influx of fluid; it occurs in hypotonic solutions due to osmotic pressure and in isotonic solutions as a result of altered permeability of the membranes of respiring mitochondria. [NIH]

Mitosis: A method of indirect cell division by means of which the two daughter nuclei normally receive identical complements of the number of chromosomes of the somatic cells of the species. [NIH]

Mobility: Capability of movement, of being moved, or of flowing freely. [EU]

Mode of Transmission: Hepatitis A [NIH]

Modeling: A treatment procedure whereby the therapist presents the target behavior which the learner is to imitate and make part of his repertoire. [NIH]

Modification: A change in an organism, or in a process in an organism, that is acquired from its own activity or environment. [NIH]

Modulator: A specific inductor that brings out characteristics peculiar to a definite region. [EU]

Molecular: Of, pertaining to, or composed of molecules : a very small mass of matter. [EU]

Molecular Evolution: Multiple rounds of selection, amplification, and mutation leading to molecules with the desired properties. [NIH]

Molecular Structure: The location of the atoms, groups or ions relative to one another in a

molecule, as well as the number, type and location of covalent bonds. [NIH]

Molecule: A chemical made up of two or more atoms. The atoms in a molecule can be the same (an oxygen molecule has two oxygen atoms) or different (a water molecule has two hydrogen atoms and one oxygen atom). Biological molecules, such as proteins and DNA, can be made up of many thousands of atoms. [NIH]

Monitor: An apparatus which automatically records such physiological signs as respiration, pulse, and blood pressure in an anesthetized patient or one undergoing surgical or other procedures. [NIH]

Monoclonal: An antibody produced by culturing a single type of cell. It therefore consists of a single species of immunoglobulin molecules. [NIH]

Monoclonal antibodies: Laboratory-produced substances that can locate and bind to cancer cells wherever they are in the body. Many monoclonal antibodies are used in cancer detection or therapy; each one recognizes a different protein on certain cancer cells. Monoclonal antibodies can be used alone, or they can be used to deliver drugs, toxins, or radioactive material directly to a tumor. [NIH]

Monocyte: A type of white blood cell. [NIH]

Mononuclear: A cell with one nucleus. [NIH]

Monotherapy: A therapy which uses only one drug. [EU]

Morphine: The principal alkaloid in opium and the prototype opiate analgesic and narcotic. Morphine has widespread effects in the central nervous system and on smooth muscle. [NIH]

Morphological: Relating to the configuration or the structure of live organs. [NIH]

Morphology: The science of the form and structure of organisms (plants, animals, and other forms of life). [NIH]

Motion Sickness: Sickness caused by motion, as sea sickness, train sickness, car sickness, and air sickness. [NIH]

Mucins: A secretion containing mucopolysaccharides and protein that is the chief constituent of mucus. [NIH]

Mucosa: A mucous membrane, or tunica mucosa. [EU]

Multiple Myeloma: A malignant tumor of plasma cells usually arising in the bone marrow; characterized by diffuse involvement of the skeletal system, hyperglobulinemia, Bence-Jones proteinuria, and anemia. [NIH]

Multiple sclerosis: A disorder of the central nervous system marked by weakness, numbness, a loss of muscle coordination, and problems with vision, speech, and bladder control. Multiple sclerosis is thought to be an autoimmune disease in which the body's immune system destroys myelin. Myelin is a substance that contains both protein and fat (lipid) and serves as a nerve insulator and helps in the transmission of nerve signals. [NIH]

Multivalent: Pertaining to a group of 5 or more homologous or partly homologous chromosomes during the zygotene stage of prophase to first metaphasis in meiosis. [NIH]

Mustard Gas: Severe irritant and vesicant of skin, eyes, and lungs. It may cause blindness and lethal lung edema and was formerly used as a war gas. The substance has been proposed as a cytostatic and for treatment of psoriasis. It has been listed as a known carcinogen in the Fourth Annual Report on Carcinogens (NTP-85-002, 1985) (Merck, 11th ed). [NIH]

Mutagen: Any agent, such as X-rays, gamma rays, mustard gas, TCDD, that can cause abnormal mutation in living cells; having the power to cause mutations. [NIH]

Mutagenesis: Process of generating genetic mutations. It may occur spontaneously or be

induced by mutagens. [NIH]

Mutate: To change the genetic material of a cell. Then changes (mutations) can be harmful, beneficial, or have no effect. [NIH]

Myalgia: Pain in a muscle or muscles. [EU]

Mycosis: Any disease caused by a fungus. [EU]

Mycosis Fungoides: A chronic malignant T-cell lymphoma of the skin. In the late stages the lymph nodes and viscera are affected. [NIH]

Myelin: The fatty substance that covers and protects nerves. [NIH]

Myelogenous: Produced by, or originating in, the bone marrow. [NIH]

Myeloma: Cancer that arises in plasma cells, a type of white blood cell. [NIH]

Myocardium: The muscle tissue of the heart composed of striated, involuntary muscle known as cardiac muscle. [NIH]

Narcotic: 1. Pertaining to or producing narcosis. 2. An agent that produces insensibility or stupor, applied especially to the opioids, i.e. to any natural or synthetic drug that has morphine-like actions. [EU]

Nasal Mucosa: The mucous membrane lining the nasal cavity. [NIH]

Nausea: An unpleasant sensation in the stomach usually accompanied by the urge to vomit. Common causes are early pregnancy, sea and motion sickness, emotional stress, intense pain, food poisoning, and various enteroviruses. [NIH]

NCI: National Cancer Institute. NCI, part of the National Institutes of Health of the United States Department of Health and Human Services, is the federal government's principal agency for cancer research. NCI conducts, coordinates, and funds cancer research, training, health information dissemination, and other programs with respect to the cause, diagnosis, prevention, and treatment of cancer. Access the NCI Web site at http://cancer.gov. [NIH]

Necrosis: A pathological process caused by the progressive degradative action of enzymes that is generally associated with severe cellular trauma. It is characterized by mitochondrial swelling, nuclear flocculation, uncontrolled cell lysis, and ultimately cell death. [NIH]

Needle Sharing: Usage of a single needle among two or more people for injecting drugs. Needle sharing is a high-risk behavior for contracting infectious disease. [NIH]

Neoplasm: A new growth of benign or malignant tissue. [NIH]

Neoplastic: Pertaining to or like a neoplasm (= any new and abnormal growth); pertaining to neoplasia (= the formation of a neoplasm). [EU]

Nerve: A cordlike structure of nervous tissue that connects parts of the nervous system with other tissues of the body and conveys nervous impulses to, or away from, these tissues. [NIH]

Nervous System: The entire nerve apparatus composed of the brain, spinal cord, nerves and ganglia. [NIH]

Neural: 1. Pertaining to a nerve or to the nerves. 2. Situated in the region of the spinal axis, as the neutral arch. [EU]

Neurologic: Having to do with nerves or the nervous system. [NIH]

Neurology: A medical specialty concerned with the study of the structures, functions, and diseases of the nervous system. [NIH]

Neuronal: Pertaining to a neuron or neurons (= conducting cells of the nervous system). [EU]

Neurons: The basic cellular units of nervous tissue. Each neuron consists of a body, an axon, and dendrites. Their purpose is to receive, conduct, and transmit impulses in the nervous

system. [NIH]

Neuropathy: A problem in any part of the nervous system except the brain and spinal cord. Neuropathies can be caused by infection, toxic substances, or disease. [NIH]

Neuroretinitis: Inflammation of the optic nerve head and adjacent retina. [NIH]

Neurotoxic: Poisonous or destructive to nerve tissue. [EU]

Neurotoxins: Toxic substances from microorganisms, plants or animals that interfere with the functions of the nervous system. Most venoms contain neurotoxic substances. Myotoxins are included in this concept. [NIH]

Neurotransmitter: Any of a group of substances that are released on excitation from the axon terminal of a presynaptic neuron of the central or peripheral nervous system and travel across the synaptic cleft to either excite or inhibit the target cell. Among the many substances that have the properties of a neurotransmitter are acetylcholine, norepinephrine, epinephrine, dopamine, glycine, y-aminobutyrate, glutamic acid, substance P, enkephalins, endorphins, and serotonin. [EU]

Neutralization: An act or process of neutralizing. [EU]

Neutrophils: Granular leukocytes having a nucleus with three to five lobes connected by slender threads of chromatin, and cytoplasm containing fine inconspicuous granules and stainable by neutral dyes. [NIH]

Nipples: The conic organs which usually give outlet to milk from the mammary glands. [NIH]

Nuclear: A test of the structure, blood flow, and function of the kidneys. The doctor injects a mildly radioactive solution into an arm vein and uses x-rays to monitor its progress through the kidneys. [NIH]

Nuclei: A body of specialized protoplasm found in nearly all cells and containing the chromosomes. [NIH]

Nucleic acid: Either of two types of macromolecule (DNA or RNA) formed by polymerization of nucleotides. Nucleic acids are found in all living cells and contain the information (genetic code) for the transfer of genetic information from one generation to the next. [NIH]

Nucleocapsid: A protein-nucleic acid complex which forms part or all of a virion. It consists of a capsid plus enclosed nucleic acid. Depending on the virus, the nucleocapsid may correspond to a naked core or be surrounded by a membranous envelope. [NIH]

Nucleolus: A small dense body (sub organelle) within the nucleus of eukaryotic cells, visible by phase contrast and interference microscopy in live cells throughout interphase. Contains RNA and protein and is the site of synthesis of ribosomal RNA. [NIH]

Nucleoprotein: Chromosomes consist largely of nuclei acids and proteins, joined here as complexes called nucleoproteins. [NIH]

Nucleus: A body of specialized protoplasm found in nearly all cells and containing the chromosomes. [NIH]

Occupational Exposure: The exposure to potentially harmful chemical, physical, or biological agents that occurs as a result of one's occupation. [NIH]

Ointments: Semisolid preparations used topically for protective emollient effects or as a vehicle for local administration of medications. Ointment bases are various mixtures of fats, waxes, animal and plant oils and solid and liquid hydrocarbons. [NIH]

Oligo: Chemical and mineral elements that exist in minimal (oligo) quantities in the body, in foods, in the air, in soil; name applied to any element observed as a microconstituent of

plant or animal tissue and of beneficial, harmful, or even doubtful significance. [NIH]

Omentum: A fold of the peritoneum (the thin tissue that lines the abdomen) that surrounds the stomach and other organs in the abdomen. [NIH]

Oncogene: A gene that normally directs cell growth. If altered, an oncogene can promote or allow the uncontrolled growth of cancer. Alterations can be inherited or caused by an environmental exposure to carcinogens. [NIH]

Opacity: Degree of density (area most dense taken for reading). [NIH]

Operon: The genetic unit consisting of a feedback system under the control of an operator gene, in which a structural gene transcribes its message in the form of mRNA upon blockade of a repressor produced by a regulator gene. Included here is the attenuator site of bacterial operons where transcription termination is regulated. [NIH]

Opiate: A remedy containing or derived from opium; also any drug that induces sleep. [EU]

Opium: The air-dried exudate from the unripe seed capsule of the opium poppy, Papaver somniferum, or its variant, P. album. It contains a number of alkaloids, but only a few - morphine, codeine, and papaverine - have clinical significance. Opium has been used as an analgesic, antitussive, antidiarrheal, and antispasmodic. [NIH]

Opportunistic Infections: An infection caused by an organism which becomes pathogenic under certain conditions, e.g., during immunosuppression. [NIH]

Optic Nerve: The 2nd cranial nerve. The optic nerve conveys visual information from the retina to the brain. The nerve carries the axons of the retinal ganglion cells which sort at the optic chiasm and continue via the optic tracts to the brain. The largest projection is to the lateral geniculate nuclei; other important targets include the superior colliculi and the suprachiasmatic nuclei. Though known as the second cranial nerve, it is considered part of the central nervous system. [NIH]

Organ Culture: The growth in aseptic culture of plant organs such as roots or shoots, beginning with organ primordia or segments and maintaining the characteristics of the organ. [NIH]

Overdose: An accidental or deliberate dose of a medication or street drug that is in excess of what is normally used. [NIH]

Ovum: A female germ cell extruded from the ovary at ovulation. [NIH]

Oxidation: The act of oxidizing or state of being oxidized. Chemically it consists in the increase of positive charges on an atom or the loss of negative charges. Most biological oxidations are accomplished by the removal of a pair of hydrogen atoms (dehydrogenation) from a molecule. Such oxidations must be accompanied by reduction of an acceptor molecule. Univalent o. indicates loss of one electron; divalent o., the loss of two electrons. [EU]

Oxidative Stress: A disturbance in the prooxidant-antioxidant balance in favor of the former, leading to potential damage. Indicators of oxidative stress include damaged DNA bases, protein oxidation products, and lipid peroxidation products (Sies, Oxidative Stress, 1991, pxv-xvi). [NIH]

Oxygenase: Enzyme which breaks down heme, the iron-containing oxygen-carrying constituent of the red blood cells. [NIH]

P53 gene: A tumor suppressor gene that normally inhibits the growth of tumors. This gene is altered in many types of cancer. [NIH]

Palate: The structure that forms the roof of the mouth. It consists of the anterior hard palate and the posterior soft palate. [NIH]

Palliative: 1. Affording relief, but not cure. 2. An alleviating medicine. [EU]

Pancreas: A mixed exocrine and endocrine gland situated transversely across the posterior abdominal wall in the epigastric and hypochondriac regions. The endocrine portion is comprised of the Islets of Langerhans, while the exocrine portion is a compound acinar gland that secretes digestive enzymes. [NIH]

Paraffin: A mixture of solid hydrocarbons obtained from petroleum. It has a wide range of uses including as a stiffening agent in ointments, as a lubricant, and as a topical anti-inflammatory. It is also commonly used as an embedding material in histology. [NIH]

Parenteral: Not through the alimentary canal but rather by injection through some other route, as subcutaneous, intramuscular, intraorbital, intracapsular, intraspinal, intrasternal, intravenous, etc. [EU]

Particle: A tiny mass of material. [EU]

Parturition: The act or process of given birth to a child. [EU]

Paternity: Establishing the father relationship of a man and a child. [NIH]

Pathogen: Any disease-producing microorganism. [EU]

Pathogenesis: The cellular events and reactions that occur in the development of disease. [NIH]

Pathologic: 1. Indicative of or caused by a morbid condition. 2. Pertaining to pathology (= branch of medicine that treats the essential nature of the disease, especially the structural and functional changes in tissues and organs of the body caused by the disease). [EU]

Pathologic Processes: The abnormal mechanisms and forms involved in the dysfunctions of tissues and organs. [NIH]

Pathophysiology: Altered functions in an individual or an organ due to disease. [NIH]

Patient Education: The teaching or training of patients concerning their own health needs. [NIH]

Penis: The external reproductive organ of males. It is composed of a mass of erectile tissue enclosed in three cylindrical fibrous compartments. Two of the three compartments, the corpus cavernosa, are placed side-by-side along the upper part of the organ. The third compartment below, the corpus spongiosum, houses the urethra. [NIH]

Peptide: Any compound consisting of two or more amino acids, the building blocks of proteins. Peptides are combined to make proteins. [NIH]

Peptide Library: A collection of cloned peptides, or chemically synthesized peptides, frequently consisting of all possible combinations of amino acids making up an n-amino acid peptide. [NIH]

Peptide Nucleic Acids: DNA analogs containing neutral amide backbone linkages composed of aminoethyl glycine units instead of the usual phosphodiester linkage of deoxyribose groups. Peptide nucleic acids have high biological stability and higher affinity for complementary DNA or RNA sequences than analogous DNA oligomers. [NIH]

Percutaneous: Performed through the skin, as injection of radiopacque material in radiological examination, or the removal of tissue for biopsy accomplished by a needle. [EU]

Pericardial Effusion: Presence of fluid within the pericardium. [NIH]

Perinatal: Pertaining to or occurring in the period shortly before and after birth; variously defined as beginning with completion of the twentieth to twenty-eighth week of gestation and ending 7 to 28 days after birth. [EU]

Peripheral blood: Blood circulating throughout the body. [NIH]

Peripheral Neuropathy: Nerve damage, usually affecting the feet and legs; causing pain, numbness, or a tingling feeling. Also called "somatic neuropathy" or "distal sensory polyneuropathy." [NIH]

Peritoneal: Having to do with the peritoneum (the tissue that lines the abdominal wall and covers most of the organs in the abdomen). [NIH]

Peritoneal Cavity: The space enclosed by the peritoneum. It is divided into two portions, the greater sac and the lesser sac or omental bursa, which lies behind the stomach. The two sacs are connected by the foramen of Winslow, or epiploic foramen. [NIH]

Peritoneal Dialysis: Dialysis fluid being introduced into and removed from the peritoneal cavity as either a continuous or an intermittent procedure. [NIH]

Peroxidase: A hemeprotein from leukocytes. Deficiency of this enzyme leads to a hereditary disorder coupled with disseminated moniliasis. It catalyzes the conversion of a donor and peroxide to an oxidized donor and water. EC 1.11.1.7. [NIH]

Peroxide: Chemical compound which contains an atom group with two oxygen atoms tied to each other. [NIH]

Pestivirus: A genus of Flaviviridae, also known as mucosal disease virus group, which is not arthropod-borne. Transmission is by direct and indirect contact, and by transplacental and congenital transmission. Species include border disease virus, bovine viral diarrhea virus, and hog cholera virus. [NIH]

Petroleum: Naturally occurring complex liquid hydrocarbons which, after distillation, yield combustible fuels, petrochemicals, and lubricants. [NIH]

Pharmacists: Those persons legally qualified by education and training to engage in the practice of pharmacy. [NIH]

Pharmacokinetic: The mathematical analysis of the time courses of absorption, distribution, and elimination of drugs. [NIH]

Pharmacologic: Pertaining to pharmacology or to the properties and reactions of drugs. [EU]

Pharynx: The hollow tube about 5 inches long that starts behind the nose and ends at the top of the trachea (windpipe) and esophagus (the tube that goes to the stomach). [NIH]

Phenotype: The outward appearance of the individual. It is the product of interactions between genes and between the genotype and the environment. This includes the killer phenotype, characteristic of yeasts. [NIH]

Phenylalanine: An aromatic amino acid that is essential in the animal diet. It is a precursor of melanin, dopamine, noradrenalin, and thyroxine. [NIH]

Phosphates: Inorganic salts of phosphoric acid. [NIH]

Phospholipids: Lipids containing one or more phosphate groups, particularly those derived from either glycerol (phosphoglycerides; glycerophospholipids) or sphingosine (sphingolipids). They are polar lipids that are of great importance for the structure and function of cell membranes and are the most abundant of membrane lipids, although not stored in large amounts in the system. [NIH]

Phosphorus: A non-metallic element that is found in the blood, muscles, nevers, bones, and teeth, and is a component of adenosine triphosphate (ATP; the primary energy source for the body's cells.) [NIH]

Phosphorylated: Attached to a phosphate group. [NIH]

Phosphorylation: The introduction of a phosphoryl group into a compound through the formation of an ester bond between the compound and a phosphorus moiety. [NIH]

Photosensitivity: An abnormal cutaneous response involving the interaction between

photosensitizing substances and sunlight or filtered or artificial light at wavelengths of 280-400 mm. There are two main types : photoallergy and photoxicity. [EU]

Physicians, Family: Those physicians who have completed the education requirements specified by the American Academy of Family Physicians. [NIH]

Physiologic: Having to do with the functions of the body. When used in the phrase "physiologic age," it refers to an age assigned by general health, as opposed to calendar age. [NIH]

Physiology: The science that deals with the life processes and functions of organismus, their cells, tissues, and organs. [NIH]

Pilot study: The initial study examining a new method or treatment. [NIH]

Plants: Multicellular, eukaryotic life forms of the kingdom Plantae. They are characterized by a mainly photosynthetic mode of nutrition; essentially unlimited growth at localized regions of cell divisions (meristems); cellulose within cells providing rigidity; the absence of organs of locomotion; absense of nervous and sensory systems; and an alteration of haploid and diploid generations. [NIH]

Plasma: The clear, yellowish, fluid part of the blood that carries the blood cells. The proteins that form blood clots are in plasma. [NIH]

Plasma cells: A type of white blood cell that produces antibodies. [NIH]

Plasmapheresis: Procedure whereby plasma is separated and extracted from anticoagulated whole blood and the red cells retransfused to the donor. Plasmapheresis is also employed for therapeutic use. [NIH]

Plasmid: An autonomously replicating, extra-chromosomal DNA molecule found in many bacteria. Plasmids are widely used as carriers of cloned genes. [NIH]

Platelet Factor 4: A high-molecular-weight proteoglycan-platelet factor complex which is released from blood platelets by thrombin. It acts as a mediator in the heparin-neutralizing capacity of the blood and plays a role in platelet aggregation. At high ionic strength (I=0.75), the complex dissociates into the active component (molecular weight 29,000) and the proteoglycan carrier (chondroitin 4-sulfate, molecular weight 350,000). The molecule exists in the form of a dimer consisting of 8 moles of platelet factor 4 and 2 moles of proteoglycan. [NIH]

Plateletpheresis: The preparation of platelet concentrates with the return of red cells and platelet-poor plasma to the donor. [NIH]

Platinum: Platinum. A heavy, soft, whitish metal, resembling tin, atomic number 78, atomic weight 195.09, symbol Pt. (From Dorland, 28th ed) It is used in manufacturing equipment for laboratory and industrial use. It occurs as a black powder (platinum black) and as a spongy substance (spongy platinum) and may have been known in Pliny's time as "alutiae". [NIH]

Pneumonia: Inflammation of the lungs. [NIH]

Point Mutation: A mutation caused by the substitution of one nucleotide for another. This results in the DNA molecule having a change in a single base pair. [NIH]

Poisoning: A condition or physical state produced by the ingestion, injection or inhalation of, or exposure to a deleterious agent. [NIH]

Polymerase: An enzyme which catalyses the synthesis of DNA using a single DNA strand as a template. The polymerase copies the template in the 5'-3'direction provided that sufficient quantities of free nucleotides, dATP and dTTP are present. [NIH]

Polymerase Chain Reaction: In vitro method for producing large amounts of specific DNA or RNA fragments of defined length and sequence from small amounts of short

oligonucleotide flanking sequences (primers). The essential steps include thermal denaturation of the double-stranded target molecules, annealing of the primers to their complementary sequences, and extension of the annealed primers by enzymatic synthesis with DNA polymerase. The reaction is efficient, specific, and extremely sensitive. Uses for the reaction include disease diagnosis, detection of difficult-to-isolate pathogens, mutation analysis, genetic testing, DNA sequencing, and analyzing evolutionary relationships. [NIH]

Polymorphism: The occurrence together of two or more distinct forms in the same population. [NIH]

Polypeptide: A peptide which on hydrolysis yields more than two amino acids; called tripeptides, tetrapeptides, etc. according to the number of amino acids contained. [EU]

Polysaccharide: A type of carbohydrate. It contains sugar molecules that are linked together chemically. [NIH]

Porphyria: A group of disorders characterized by the excessive production of porphyrins or their precursors that arises from abnormalities in the regulation of the porphyrin-heme pathway. The porphyrias are usually divided into three broad groups, erythropoietic, hepatic, and erythrohepatic, according to the major sites of abnormal porphyrin synthesis. [NIH]

Porphyria Cutanea Tarda: A form of hepatic porphyria (porphyria, hepatic) characterized by photosensitivity resulting in bullae that rupture easily to form shallow ulcers. This condition occurs in two forms: a sporadic, nonfamilial form that begins in middle age and has normal amounts of uroporphyrinogen decarboxylase with diminished activity in the liver; and a familial form in which there is an autosomal dominant inherited deficiency of uroporphyrinogen decarboxylase in the liver and red blood cells. [NIH]

Porphyria, Hepatic: Porphyria in which the liver is the site where excess formation of porphyrin or its precursors is found. Acute intermittent porphyria and porphyria cutanea tarda are types of hepatic porphyria. [NIH]

Porphyrins: A group of compounds containing the porphin structure, four pyrrole rings connected by methine bridges in a cyclic configuration to which a variety of side chains are attached. The nature of the side chain is indicated by a prefix, as uroporphyrin, hematoporphyrin, etc. The porphyrins, in combination with iron, form the heme component in biologically significant compounds such as hemoglobin and myoglobin. [NIH]

Portal Hypertension: High blood pressure in the portal vein. This vein carries blood into the liver. Portal hypertension is caused by a blood clot. This is a common complication of cirrhosis. [NIH]

Posterior: Situated in back of, or in the back part of, or affecting the back or dorsal surface of the body. In lower animals, it refers to the caudal end of the body. [EU]

Postherpetic Neuralgia: Variety of neuralgia associated with migraine in which pain is felt in or behind the eye. [NIH]

Postnatal: Occurring after birth, with reference to the newborn. [EU]

Post-translational: The cleavage of signal sequence that directs the passage of the protein through a cell or organelle membrane. [NIH]

Potentiates: A degree of synergism which causes the exposure of the organism to a harmful substance to worsen a disease already contracted. [NIH]

Practicability: A non-standard characteristic of an analytical procedure. It is dependent on the scope of the method and is determined by requirements such as sample throughout and costs. [NIH]

Practice Guidelines: Directions or principles presenting current or future rules of policy for

the health care practitioner to assist him in patient care decisions regarding diagnosis, therapy, or related clinical circumstances. The guidelines may be developed by government agencies at any level, institutions, professional societies, governing boards, or by the convening of expert panels. The guidelines form a basis for the evaluation of all aspects of health care and delivery. [NIH]

Preclinical: Before a disease becomes clinically recognizable. [EU]

Precursor: Something that precedes. In biological processes, a substance from which another, usually more active or mature substance is formed. In clinical medicine, a sign or symptom that heralds another. [EU]

Predictive factor: A situation or condition that may increase a person's risk of developing a certain disease or disorder. [NIH]

Predisposition: A latent susceptibility to disease which may be activated under certain conditions, as by stress. [EU]

Prenatal: Existing or occurring before birth, with reference to the fetus. [EU]

Prepuce: A covering fold of skin; often used alone to designate the preputium penis. [EU]

Prevalence: The total number of cases of a given disease in a specified population at a designated time. It is differentiated from incidence, which refers to the number of new cases in the population at a given time. [NIH]

Primary Biliary Cirrhosis: A chronic liver disease. Slowly destroys the bile ducts in the liver. This prevents release of bile. Long-term irritation of the liver may cause scarring and cirrhosis in later stages of the disease. [NIH]

Primary Prevention: Prevention of disease or mental disorders in susceptible individuals or populations through promotion of health, including mental health, and specific protection, as in immunization, as distinguished from the prevention of complications or after-effects of existing disease. [NIH]

Primary Sclerosing Cholangitis: Irritation, scarring, and narrowing of the bile ducts inside and outside the liver. Bile builds up in the liver and may damage its cells. Many people with this condition also have ulcerative colitis. [NIH]

Probe: An instrument used in exploring cavities, or in the detection and dilatation of strictures, or in demonstrating the potency of channels; an elongated instrument for exploring or sounding body cavities. [NIH]

Prodrug: A substance that gives rise to a pharmacologically active metabolite, although not itself active (i. e. an inactive precursor). [NIH]

Progesterone: Pregn-4-ene-3,20-dione. The principal progestational hormone of the body, secreted by the corpus luteum, adrenal cortex, and placenta. Its chief function is to prepare the uterus for the reception and development of the fertilized ovum. It acts as an antiovulatory agent when administered on days 5-25 of the menstrual cycle. [NIH]

Prognostic factor: A situation or condition, or a characteristic of a patient, that can be used to estimate the chance of recovery from a disease, or the chance of the disease recurring (coming back). [NIH]

Progression: Increase in the size of a tumor or spread of cancer in the body. [NIH]

Progressive: Advancing; going forward; going from bad to worse; increasing in scope or severity. [EU]

Progressive disease: Cancer that is increasing in scope or severity. [NIH]

Projection: A defense mechanism, operating unconsciously, whereby that which is emotionally unacceptable in the self is rejected and attributed (projected) to others. [NIH]

Promoter: A chemical substance that increases the activity of a carcinogenic process. [NIH]

Promotor: In an operon, a nucleotide sequence located at the operator end which contains all the signals for the correct initiation of genetic transcription by the RNA polymerase holoenzyme and determines the maximal rate of RNA synthesis. [NIH]

Prone: Having the front portion of the body downwards. [NIH]

Prophase: The first phase of cell division, in which the chromosomes become visible, the nucleus starts to lose its identity, the spindle appears, and the centrioles migrate toward opposite poles. [NIH]

Prophylaxis: An attempt to prevent disease. [NIH]

Prospective Studies: Observation of a population for a sufficient number of persons over a sufficient number of years to generate incidence or mortality rates subsequent to the selection of the study group. [NIH]

Prospective study: An epidemiologic study in which a group of individuals (a cohort), all free of a particular disease and varying in their exposure to a possible risk factor, is followed over a specific amount of time to determine the incidence rates of the disease in the exposed and unexposed groups. [NIH]

Prostate: A gland in males that surrounds the neck of the bladder and the urethra. It secretes a substance that liquifies coagulated semen. It is situated in the pelvic cavity behind the lower part of the pubic symphysis, above the deep layer of the triangular ligament, and rests upon the rectum. [NIH]

Protease: Proteinase (= any enzyme that catalyses the splitting of interior peptide bonds in a protein). [EU]

Protease Inhibitors: Compounds which inhibit or antagonize biosynthesis or actions of proteases (endopeptidases). [NIH]

Protein Binding: The process in which substances, either endogenous or exogenous, bind to proteins, peptides, enzymes, protein precursors, or allied compounds. Specific protein-binding measures are often used as assays in diagnostic assessments. [NIH]

Protein C: A vitamin-K dependent zymogen present in the blood, which, upon activation by thrombin and thrombomodulin exerts anticoagulant properties by inactivating factors Va and VIIIa at the rate-limiting steps of thrombin formation. [NIH]

Protein Conformation: The characteristic 3-dimensional shape of a protein, including the secondary, supersecondary (motifs), tertiary (domains) and quaternary structure of the peptide chain. Quaternary protein structure describes the conformation assumed by multimeric proteins (aggregates of more than one polypeptide chain). [NIH]

Protein S: The vitamin K-dependent cofactor of activated protein C. Together with protein C, it inhibits the action of factors VIIIa and Va. A deficiency in protein S can lead to recurrent venous and arterial thrombosis. [NIH]

Proteins: Polymers of amino acids linked by peptide bonds. The specific sequence of amino acids determines the shape and function of the protein. [NIH]

Proteinuria: The presence of protein in the urine, indicating that the kidneys are not working properly. [NIH]

Proteolytic: 1. Pertaining to, characterized by, or promoting proteolysis. 2. An enzyme that promotes proteolysis (= the splitting of proteins by hydrolysis of the peptide bonds with formation of smaller polypeptides). [EU]

Proteome: The protein complement of an organism coded for by its genome. [NIH]

Protocol: The detailed plan for a clinical trial that states the trial's rationale, purpose, drug or

vaccine dosages, length of study, routes of administration, who may participate, and other aspects of trial design. [NIH]

Protons: Stable elementary particles having the smallest known positive charge, found in the nuclei of all elements. The proton mass is less than that of a neutron. A proton is the nucleus of the light hydrogen atom, i.e., the hydrogen ion. [NIH]

Protozoa: A subkingdom consisting of unicellular organisms that are the simplest in the animal kingdom. Most are free living. They range in size from submicroscopic to macroscopic. Protozoa are divided into seven phyla: Sarcomastigophora, Labyrinthomorpha, Apicomplexa, Microspora, Ascetospora, Myxozoa, and Ciliophora. [NIH]

Pruritic: Pertaining to or characterized by pruritus. [EU]

Psoriasis: A common genetically determined, chronic, inflammatory skin disease characterized by rounded erythematous, dry, scaling patches. The lesions have a predilection for nails, scalp, genitalia, extensor surfaces, and the lumbosacral region. Accelerated epidermopoiesis is considered to be the fundamental pathologic feature in psoriasis. [NIH]

Psychiatric: Pertaining to or within the purview of psychiatry. [EU]

Psychic: Pertaining to the psyche or to the mind; mental. [EU]

Psychoactive: Those drugs which alter sensation, mood, consciousness or other psychological or behavioral functions. [NIH]

Public Health: Branch of medicine concerned with the prevention and control of disease and disability, and the promotion of physical and mental health of the population on the international, national, state, or municipal level. [NIH]

Public Policy: A course or method of action selected, usually by a government, from among alternatives to guide and determine present and future decisions. [NIH]

Publishing: "The business or profession of the commercial production and issuance of literature" (Webster's 3d). It includes the publisher, publication processes, editing and editors. Production may be by conventional printing methods or by electronic publishing. [NIH]

Pulmonary: Relating to the lungs. [NIH]

Pulmonary Edema: An accumulation of an excessive amount of watery fluid in the lungs, may be caused by acute exposure to dangerous concentrations of irritant gasses. [NIH]

Pulse: The rhythmical expansion and contraction of an artery produced by waves of pressure caused by the ejection of blood from the left ventricle of the heart as it contracts. [NIH]

Purines: A series of heterocyclic compounds that are variously substituted in nature and are known also as purine bases. They include adenine and guanine, constituents of nucleic acids, as well as many alkaloids such as caffeine and theophylline. Uric acid is the metabolic end product of purine metabolism. [NIH]

Puromycin: An antibiotic from Streptomyces alboniger that inhibits protein synthesis by binding to RNA. It is a antineoplastic and antitrypanosomal agent and is used in research as an inhibitor of protein synthesis. [NIH]

Pustular: Pertaining to or of the nature of a pustule; consisting of pustules (= a visible collection of pus within or beneath the epidermis). [EU]

Pyridoxal: 3-Hydroxy-5-(hydroxymethyl)-2-methyl-4- pyridinecarboxaldehyde. [NIH]

Pyrimidines: A family of 6-membered heterocyclic compounds occurring in nature in a wide variety of forms. They include several nucleic acid constituents (cytosine, thymine, and

uracil) and form the basic structure of the barbiturates. [NIH]

Quality of Life: A generic concept reflecting concern with the modification and enhancement of life attributes, e.g., physical, political, moral and social environment. [NIH]

Quiescent: Marked by a state of inactivity or repose. [EU]

Race: A population within a species which exhibits general similarities within itself, but is both discontinuous and distinct from other populations of that species, though not sufficiently so as to achieve the status of a taxon. [NIH]

Radiation: Emission or propagation of electromagnetic energy (waves/rays), or the waves/rays themselves; a stream of electromagnetic particles (electrons, neutrons, protons, alpha particles) or a mixture of these. The most common source is the sun. [NIH]

Radiation therapy: The use of high-energy radiation from x-rays, gamma rays, neutrons, and other sources to kill cancer cells and shrink tumors. Radiation may come from a machine outside the body (external-beam radiation therapy), or it may come from radioactive material placed in the body in the area near cancer cells (internal radiation therapy, implant radiation, or brachytherapy). Systemic radiation therapy uses a radioactive substance, such as a radiolabeled monoclonal antibody, that circulates throughout the body. Also called radiotherapy. [NIH]

Radioactive: Giving off radiation. [NIH]

Radioimmunotherapy: Radiotherapy where cytotoxic radionuclides are linked to antibodies in order to deliver toxins directly to tumor targets. Therapy with targeted radiation rather than antibody-targeted toxins (immunotoxins) has the advantage that adjacent tumor cells, which lack the appropriate antigenic determinants, can be destroyed by radiation cross-fire. Radioimmunotherapy is sometimes called targeted radiotherapy, but this latter term can also refer to radionuclides linked to non-immune molecules (radiotherapy). [NIH]

Radiological: Pertaining to radiodiagnostic and radiotherapeutic procedures, and interventional radiology or other planning and guiding medical radiology. [NIH]

Radiology: A specialty concerned with the use of x-ray and other forms of radiant energy in the diagnosis and treatment of disease. [NIH]

Radiotherapy: The use of ionizing radiation to treat malignant neoplasms and other benign conditions. The most common forms of ionizing radiation used as therapy are x-rays, gamma rays, and electrons. A special form of radiotherapy, targeted radiotherapy, links a cytotoxic radionuclide to a molecule that targets the tumor. When this molecule is an antibody or other immunologic molecule, the technique is called radioimmunotherapy. [NIH]

Randomized: Describes an experiment or clinical trial in which animal or human subjects are assigned by chance to separate groups that compare different treatments. [NIH]

Reactive Oxygen Species: Reactive intermediate oxygen species including both radicals and non-radicals. These substances are constantly formed in the human body and have been shown to kill bacteria and inactivate proteins, and have been implicated in a number of diseases. Scientific data exist that link the reactive oxygen species produced by inflammatory phagocytes to cancer development. [NIH]

Reagent: A substance employed to produce a chemical reaction so as to detect, measure, produce, etc., other substances. [EU]

Receptor: A molecule inside or on the surface of a cell that binds to a specific substance and causes a specific physiologic effect in the cell. [NIH]

Recombinant: A cell or an individual with a new combination of genes not found together in either parent; usually applied to linked genes. [EU]

Recombinant Proteins: Proteins prepared by recombinant DNA technology. [NIH]

Recombination: The formation of new combinations of genes as a result of segregation in crosses between genetically different parents; also the rearrangement of linked genes due to crossing-over. [NIH]

Rectum: The last 8 to 10 inches of the large intestine. [NIH]

Recurrence: The return of a sign, symptom, or disease after a remission. [NIH]

Red blood cells: RBCs. Cells that carry oxygen to all parts of the body. Also called erythrocytes. [NIH]

Reentry: Reexcitation caused by continuous propagation of the same impulse for one or more cycles. [NIH]

Refer: To send or direct for treatment, aid, information, de decision. [NIH]

Refraction: A test to determine the best eyeglasses or contact lenses to correct a refractive error (myopia, hyperopia, or astigmatism). [NIH]

Refractory: Not readily yielding to treatment. [EU]

Regeneration: The natural renewal of a structure, as of a lost tissue or part. [EU]

Regimen: A treatment plan that specifies the dosage, the schedule, and the duration of treatment. [NIH]

Regression Analysis: Procedures for finding the mathematical function which best describes the relationship between a dependent variable and one or more independent variables. In linear regression (see linear models) the relationship is constrained to be a straight line and least-squares analysis is used to determine the best fit. In logistic regression (see logistic models) the dependent variable is qualitative rather than continuously variable and likelihood functions are used to find the best relationship. In multiple regression the dependent variable is considered to depend on more than a single independent variable. [NIH]

Relapse: The return of signs and symptoms of cancer after a period of improvement. [NIH]

Reliability: Used technically, in a statistical sense, of consistency of a test with itself, i. e. the extent to which we can assume that it will yield the same result if repeated a second time. [NIH]

Remission: A decrease in or disappearance of signs and symptoms of cancer. In partial remission, some, but not all, signs and symptoms of cancer have disappeared. In complete remission, all signs and symptoms of cancer have disappeared, although there still may be cancer in the body. [NIH]

Renal capsule: The fibrous connective tissue that surrounds each kidney. [NIH]

Renal Dialysis: Removal of certain elements from the blood based on the difference in their rates of diffusion through a semipermeable membrane. [NIH]

Replicon: In order to be replicated, DNA molecules must contain an origin of duplication and in bacteria and viruses there is usually only one per genome. Such molecules are called replicons. [NIH]

Resection: Removal of tissue or part or all of an organ by surgery. [NIH]

Respiration: The act of breathing with the lungs, consisting of inspiration, or the taking into the lungs of the ambient air, and of expiration, or the expelling of the modified air which contains more carbon dioxide than the air taken in (Blakiston's Gould Medical Dictionary, 4th ed.). This does not include tissue respiration (= oxygen consumption) or cell respiration (= cell respiration). [NIH]

Response rate: The percentage of patients whose cancer shrinks or disappears after

treatment. [NIH]

Retina: The ten-layered nervous tissue membrane of the eye. It is continuous with the optic nerve and receives images of external objects and transmits visual impulses to the brain. Its outer surface is in contact with the choroid and the inner surface with the vitreous body. The outer-most layer is pigmented, whereas the inner nine layers are transparent. [NIH]

Retinal: 1. Pertaining to the retina. 2. The aldehyde of retinol, derived by the oxidative enzymatic splitting of absorbed dietary carotene, and having vitamin A activity. In the retina, retinal combines with opsins to form visual pigments. One isomer, 11-cis retinal combines with opsin in the rods (scotopsin) to form rhodopsin, or visual purple. Another, all-trans retinal (trans-r.); visual yellow; xanthopsin) results from the bleaching of rhodopsin by light, in which the 11-cis form is converted to the all-trans form. Retinal also combines with opsins in the cones (photopsins) to form the three pigments responsible for colour vision. Called also retinal, and retinene1. [EU]

Retinitis: Inflammation of the retina. It is rarely limited to the retina, but is commonly associated with diseases of the choroid (chorioretinitis) and of the optic nerve (neuroretinitis). The disease may be confined to one eye, but since it is generally dependent on a constitutional factor, it is almost always bilateral. It may be acute in course, but as a rule it lasts many weeks or even several months. [NIH]

Retreatment: The therapy of the same disease in a patient, with the same agent or procedure repeated after initial treatment, or with an additional or alternate measure or follow-up. It does not include therapy which requires more than one administration of a therapeutic agent or regimen. Retreatment is often used with reference to a different modality when the original one was inadequate, harmful, or unsuccessful. [NIH]

Retrospective: Looking back at events that have already taken place. [NIH]

Retroviral vector: RNA from a virus that is used to insert genetic material into cells. [NIH]

Reversion: A return to the original condition, e. g. the reappearance of the normal or wild type in previously mutated cells, tissues, or organisms. [NIH]

Rheumatism: A group of disorders marked by inflammation or pain in the connective tissue structures of the body. These structures include bone, cartilage, and fat. [NIH]

Rheumatoid: Resembling rheumatism. [EU]

Rheumatoid arthritis: A form of arthritis, the cause of which is unknown, although infection, hypersensitivity, hormone imbalance and psychologic stress have been suggested as possible causes. [NIH]

Ribavirin: 1-beta-D-Ribofuranosyl-1H-1,2,4-triazole-3-carboxamide. A nucleoside antimetabolite antiviral agent that blocks nucleic acid synthesis and is used against both RNA and DNA viruses. [NIH]

Riboflavin: Nutritional factor found in milk, eggs, malted barley, liver, kidney, heart, and leafy vegetables. The richest natural source is yeast. It occurs in the free form only in the retina of the eye, in whey, and in urine; its principal forms in tissues and cells are as FMN and FAD. [NIH]

Ribosome: A granule of protein and RNA, synthesized in the nucleolus and found in the cytoplasm of cells. Ribosomes are the main sites of protein synthesis. Messenger RNA attaches to them and there receives molecules of transfer RNA bearing amino acids. [NIH]

Rickettsiae: One of a group of obligate intracellular parasitic microorganisms, once regarded as intermediate in their properties between bacteria and viruses but now classified as bacteria in the order Rickettsiales, which includes 17 genera and 3 families: Rickettsiace. [NIH]

Rimantadine: An RNA synthesis inhibitor that is used as an antiviral agent in the prophylaxis and treatment of influenza. [NIH]

Risk factor: A habit, trait, condition, or genetic alteration that increases a person's chance of developing a disease. [NIH]

Rod: A reception for vision, located in the retina. [NIH]

Rubella: An acute, usually benign, infectious disease caused by a togavirus and most often affecting children and nonimmune young adults, in which the virus enters the respiratory tract via droplet nuclei and spreads to the lymphatic system. It is characterized by a slight cold, sore throat, and fever, followed by enlargement of the postauricular, suboccipital, and cervical lymph nodes, and the appearances of a fine pink rash that begins on the head and spreads to become generalized. Called also German measles, roetln, röteln, and three-day measles, and rubeola in French and Spanish. [EU]

Saliva: The clear, viscous fluid secreted by the salivary glands and mucous glands of the mouth. It contains mucins, water, organic salts, and ptylin. [NIH]

Salivary: The duct that convey saliva to the mouth. [NIH]

Salivary glands: Glands in the mouth that produce saliva. [NIH]

Salvage Therapy: A therapeutic approach, involving chemotherapy, radiation therapy, or surgery, after initial regimens have failed to lead to improvement in a patient's condition. Salvage therapy is most often used for neoplastic diseases. [NIH]

Sanitation: The development and establishment of environmental conditions favorable to the health of the public. [NIH]

Saponins: Sapogenin glycosides. A type of glycoside widely distributed in plants. Each consists of a sapogenin as the aglycon moiety, and a sugar. The sapogenin may be a steroid or a triterpene and the sugar may be glucose, galactose, a pentose, or a methylpentose. Sapogenins are poisonous towards the lower forms of life and are powerful hemolytics when injected into the blood stream able to dissolve red blood cells at even extreme dilutions. [NIH]

Sarcoma: A connective tissue neoplasm formed by proliferation of mesodermal cells; it is usually highly malignant. [NIH]

Satellite: Applied to a vein which closely accompanies an artery for some distance; in cytogenetics, a chromosomal agent separated by a secondary constriction from the main body of the chromosome. [NIH]

Schizoid: Having qualities resembling those found in greater degree in schizophrenics; a person of schizoid personality. [NIH]

Schizophrenia: A mental disorder characterized by a special type of disintegration of the personality. [NIH]

Schizotypal Personality Disorder: A personality disorder in which there are oddities of thought (magical thinking, paranoid ideation, suspiciousness), perception (illusions, depersonalization), speech (digressive, vague, overelaborate), and behavior (inappropriate affect in social interactions, frequently social isolation) that are not severe enough to characterize schizophrenia. [NIH]

Sclerosis: A pathological process consisting of hardening or fibrosis of an anatomical structure, often a vessel or a nerve. [NIH]

Screening: Checking for disease when there are no symptoms. [NIH]

Secretion: 1. The process of elaborating a specific product as a result of the activity of a gland; this activity may range from separating a specific substance of the blood to the

elaboration of a new chemical substance. 2. Any substance produced by secretion. [EU]

Sedimentation: The act of causing the deposit of sediment, especially by the use of a centrifugal machine. [EU]

Segregation: The separation in meiotic cell division of homologous chromosome pairs and their contained allelomorphic gene pairs. [NIH]

Selenium: An element with the atomic symbol Se, atomic number 34, and atomic weight 78.96. It is an essential micronutrient for mammals and other animals but is toxic in large amounts. Selenium protects intracellular structures against oxidative damage. It is an essential component of glutathione peroxidase. [NIH]

Semen: The thick, yellowish-white, viscid fluid secretion of male reproductive organs discharged upon ejaculation. In addition to reproductive organ secretions, it contains spermatozoa and their nutrient plasma. [NIH]

Senescence: The bodily and mental state associated with advancing age. [NIH]

Sequela: Any lesion or affection following or caused by an attack of disease. [EU]

Sequence Analysis: A multistage process that includes the determination of a sequence (protein, carbohydrate, etc.), its fragmentation and analysis, and the interpretation of the resulting sequence information. [NIH]

Sequencing: The determination of the order of nucleotides in a DNA or RNA chain. [NIH]

Serine: A non-essential amino acid occurring in natural form as the L-isomer. It is synthesized from glycine or threonine. It is involved in the biosynthesis of purines, pyrimidines, and other amino acids. [NIH]

Seroconversion: The change of a serologic test from negative to positive, indicating the development of antibodies in response to infection or immunization. [EU]

Serologic: Analysis of a person's serum, especially specific immune or lytic serums. [NIH]

Serologic Tests: Diagnostic procedures involving immunoglobulin reactions. [NIH]

Serology: The study of serum, especially of antigen-antibody reactions in vitro. [NIH]

Serotypes: A cause of haemorrhagic septicaemia (in cattle, sheep and pigs), fowl cholera of birds, pasteurellosis of rabbits, and gangrenous mastitis of ewes. It is also commonly found in atrophic rhinitis of pigs. [NIH]

Serous: Having to do with serum, the clear liquid part of blood. [NIH]

Serum: The clear liquid part of the blood that remains after blood cells and clotting proteins have been removed. [NIH]

Sexual Partners: Married or single individuals who share sexual relations. [NIH]

Sexually Transmitted Diseases: Diseases due to or propagated by sexual contact. [NIH]

Shedding: Release of infectious particles (e. g., bacteria, viruses) into the environment, for example by sneezing, by fecal excretion, or from an open lesion. [NIH]

Shock: The general bodily disturbance following a severe injury; an emotional or moral upset occasioned by some disturbing or unexpected experience; disruption of the circulation, which can upset all body functions: sometimes referred to as circulatory shock. [NIH]

Side effect: A consequence other than the one(s) for which an agent or measure is used, as the adverse effects produced by a drug, especially on a tissue or organ system other than the one sought to be benefited by its administration. [EU]

Signs and Symptoms: Clinical manifestations that can be either objective when observed by a physician, or subjective when perceived by the patient. [NIH]

Skeletal: Having to do with the skeleton (boney part of the body). [NIH]

Skull: The skeleton of the head including the bones of the face and the bones enclosing the brain. [NIH]

Small intestine: The part of the digestive tract that is located between the stomach and the large intestine. [NIH]

Smallpox: A generalized virus infection with a vesicular rash. [NIH]

Smooth muscle: Muscle that performs automatic tasks, such as constricting blood vessels. [NIH]

Sneezing: Sudden, forceful, involuntary expulsion of air from the nose and mouth caused by irritation to the mucous membranes of the upper respiratory tract. [NIH]

Social Environment: The aggregate of social and cultural institutions, forms, patterns, and processes that influence the life of an individual or community. [NIH]

Social Support: Support systems that provide assistance and encouragement to individuals with physical or emotional disabilities in order that they may better cope. Informal social support is usually provided by friends, relatives, or peers, while formal assistance is provided by churches, groups, etc. [NIH]

Soft tissue: Refers to muscle, fat, fibrous tissue, blood vessels, or other supporting tissue of the body. [NIH]

Solid tumor: Cancer of body tissues other than blood, bone marrow, or the lymphatic system. [NIH]

Solvent: 1. Dissolving; effecting a solution. 2. A liquid that dissolves or that is capable of dissolving; the component of a solution that is present in greater amount. [EU]

Somatic: 1. Pertaining to or characteristic of the soma or body. 2. Pertaining to the body wall in contrast to the viscera. [EU]

Somatic cells: All the body cells except the reproductive (germ) cells. [NIH]

Specialist: In medicine, one who concentrates on 1 special branch of medical science. [NIH]

Species: A taxonomic category subordinate to a genus (or subgenus) and superior to a subspecies or variety, composed of individuals possessing common characters distinguishing them from other categories of individuals of the same taxonomic level. In taxonomic nomenclature, species are designated by the genus name followed by a Latin or Latinized adjective or noun. [EU]

Specificity: Degree of selectivity shown by an antibody with respect to the number and types of antigens with which the antibody combines, as well as with respect to the rates and the extents of these reactions. [NIH]

Specimen Handling: Procedures for collecting, preserving, and transporting of specimens sufficiently stable to provide accurate and precise results suitable for clinical interpretation. [NIH]

Spectrum: A charted band of wavelengths of electromagnetic vibrations obtained by refraction and diffraction. By extension, a measurable range of activity, such as the range of bacteria affected by an antibiotic (antibacterial s.) or the complete range of manifestations of a disease. [EU]

Sperm: The fecundating fluid of the male. [NIH]

Spermatozoa: Mature male germ cells that develop in the seminiferous tubules of the testes. Each consists of a head, a body, and a tail that provides propulsion. The head consists mainly of chromatin. [NIH]

Spinal cord: The main trunk or bundle of nerves running down the spine through holes in

the spinal bone (the vertebrae) from the brain to the level of the lower back. [NIH]

Spirochete: Lyme disease. [NIH]

Spleen: An organ that is part of the lymphatic system. The spleen produces lymphocytes, filters the blood, stores blood cells, and destroys old blood cells. It is located on the left side of the abdomen near the stomach. [NIH]

Sporadic: Neither endemic nor epidemic; occurring occasionally in a random or isolated manner. [EU]

Stabilization: The creation of a stable state. [EU]

Staging: Performing exams and tests to learn the extent of the cancer within the body, especially whether the disease has spread from the original site to other parts of the body. [NIH]

Standard therapy: A currently accepted and widely used treatment for a certain type of cancer, based on the results of past research. [NIH]

Statistically significant: Describes a mathematical measure of difference between groups. The difference is said to be statistically significant if it is greater than what might be expected to happen by chance alone. [NIH]

Steatosis: Fatty degeneration. [EU]

Stellate: Star shaped. [NIH]

Stem Cells: Relatively undifferentiated cells of the same lineage (family type) that retain the ability to divide and cycle throughout postnatal life to provide cells that can become specialized and take the place of those that die or are lost. [NIH]

Stenosis: Narrowing or stricture of a duct or canal. [EU]

Sterile: Unable to produce children. [NIH]

Steroid: A group name for lipids that contain a hydrogenated cyclopentanoperhydrophenanthrene ring system. Some of the substances included in this group are progesterone, adrenocortical hormones, the gonadal hormones, cardiac aglycones, bile acids, sterols (such as cholesterol), toad poisons, saponins, and some of the carcinogenic hydrocarbons. [EU]

Stimulus: That which can elicit or evoke action (response) in a muscle, nerve, gland or other excitable issue, or cause an augmenting action upon any function or metabolic process. [NIH]

Stomach: An organ of digestion situated in the left upper quadrant of the abdomen between the termination of the esophagus and the beginning of the duodenum. [NIH]

Stomatitis: Inflammation of the oral mucosa, due to local or systemic factors which may involve the buccal and labial mucosa, palate, tongue, floor of the mouth, and the gingivae. [EU]

Strand: DNA normally exists in the bacterial nucleus in a helix, in which two strands are coiled together. [NIH]

Street Drugs: Drugs obtained and often manufactured illegally for the subjective effects they are said to produce. They are often distributed in urban areas, but are also available in suburban and rural areas, and tend to be grossly impure and may cause unexpected toxicity. [NIH]

Stress: Forcibly exerted influence; pressure. Any condition or situation that causes strain or tension. Stress may be either physical or psychologic, or both. [NIH]

Stress management: A set of techniques used to help an individual cope more effectively with difficult situations in order to feel better emotionally, improve behavioral skills, and often to enhance feelings of control. Stress management may include relaxation exercises,

assertiveness training, cognitive restructuring, time management, and social support. It can be delivered either on a one-to-one basis or in a group format. [NIH]

Stricture: The abnormal narrowing of a body opening. Also called stenosis. [NIH]

Stroke: Sudden loss of function of part of the brain because of loss of blood flow. Stroke may be caused by a clot (thrombosis) or rupture (hemorrhage) of a blood vessel to the brain. [NIH]

Subacute: Somewhat acute; between acute and chronic. [EU]

Subclinical: Without clinical manifestations; said of the early stage(s) of an infection or other disease or abnormality before symptoms and signs become apparent or detectable by clinical examination or laboratory tests, or of a very mild form of an infection or other disease or abnormality. [EU]

Subcutaneous: Beneath the skin. [NIH]

Subspecies: A category intermediate in rank between species and variety, based on a smaller number of correlated characters than are used to differentiate species and generally conditioned by geographical and/or ecological occurrence. [NIH]

Substance P: An eleven-amino acid neurotransmitter that appears in both the central and peripheral nervous systems. It is involved in transmission of pain, causes rapid contractions of the gastrointestinal smooth muscle, and modulates inflammatory and immune responses. [NIH]

Substrate: A substance upon which an enzyme acts. [EU]

Sulfur: An element that is a member of the chalcogen family. It has an atomic symbol S, atomic number 16, and atomic weight 32.066. It is found in the amino acids cysteine and methionine. [NIH]

Superinfection: A frequent complication of drug therapy for microbial infection. It may result from opportunistic colonization following immunosuppression by the primary pathogen and can be influenced by the time interval between infections, microbial physiology, or host resistance. Experimental challenge and in vitro models are sometimes used in virulence and infectivity studies. [NIH]

Superoxide: Derivative of molecular oxygen that can damage cells. [NIH]

Superoxide Dismutase: An oxidoreductase that catalyzes the reaction between superoxide anions and hydrogen to yield molecular oxygen and hydrogen peroxide. The enzyme protects the cell against dangerous levels of superoxide. EC 1.15.1.1. [NIH]

Supplementation: Adding nutrients to the diet. [NIH]

Support group: A group of people with similar disease who meet to discuss how better to cope with their cancer and treatment. [NIH]

Suppression: A conscious exclusion of disapproved desire contrary with repression, in which the process of exclusion is not conscious. [NIH]

Surfactant: A fat-containing protein in the respiratory passages which reduces the surface tension of pulmonary fluids and contributes to the elastic properties of pulmonary tissue. [NIH]

Symptomatic: Having to do with symptoms, which are signs of a condition or disease. [NIH]

Symptomatic treatment: Therapy that eases symptoms without addressing the cause of disease. [NIH]

Symptomatology: 1. That branch of medicine with treats of symptoms; the systematic discussion of symptoms. 2. The combined symptoms of a disease. [EU]

Synergistic: Acting together; enhancing the effect of another force or agent. [EU]

Syphilis: A contagious venereal disease caused by the spirochete Treponema pallidum. [NIH]

Systemic: Affecting the entire body. [NIH]

Systemic disease: Disease that affects the whole body. [NIH]

Systemic lupus erythematosus: SLE. A chronic inflammatory connective tissue disease marked by skin rashes, joint pain and swelling, inflammation of the kidneys, inflammation of the fibrous tissue surrounding the heart (i.e., the pericardium), as well as other problems. Not all affected individuals display all of these problems. May be referred to as lupus. [NIH]

Systemic therapy: Treatment that uses substances that travel through the bloodstream, reaching and affecting cells all over the body. [NIH]

Tamponade: The inserting of a tampon; a dressing is inserted firmly into a wound or body cavity, as the nose, uterus or vagina, principally for stopping hemorrhage. [NIH]

Telomere: A terminal section of a chromosome which has a specialized structure and which is involved in chromosomal replication and stability. Its length is believed to be a few hundred base pairs. [NIH]

Temporal: One of the two irregular bones forming part of the lateral surfaces and base of the skull, and containing the organs of hearing. [NIH]

Tetani: Causal agent of tetanus. [NIH]

Tetanic: Having the characteristics of, or relating to tetanus. [NIH]

Tetanus: A disease caused by tetanospasmin, a powerful protein toxin produced by Clostridium tetani. Tetanus usually occurs after an acute injury, such as a puncture wound or laceration. Generalized tetanus, the most common form, is characterized by tetanic muscular contractions and hyperreflexia. Localized tetanus presents itself as a mild condition with manifestations restricted to muscles near the wound. It may progress to the generalized form. [NIH]

Thalassemia: A group of hereditary hemolytic anemias in which there is decreased synthesis of one or more hemoglobin polypeptide chains. There are several genetic types with clinical pictures ranging from barely detectable hematologic abnormality to severe and fatal anemia. [NIH]

Therapeutics: The branch of medicine which is concerned with the treatment of diseases, palliative or curative. [NIH]

Thermal: Pertaining to or characterized by heat. [EU]

Threonine: An essential amino acid occurring naturally in the L-form, which is the active form. It is found in eggs, milk, gelatin, and other proteins. [NIH]

Thrombin: An enzyme formed from prothrombin that converts fibrinogen to fibrin. (Dorland, 27th ed) EC 3.4.21.5. [NIH]

Thrombocytopenia: A decrease in the number of blood platelets. [NIH]

Thrombomodulin: A cell surface glycoprotein of endothelial cells that binds thrombin and serves as a cofactor in the activation of protein C and its regulation of blood coagulation. [NIH]

Thrombopenia: Reduction in the number of platelets in the blood. [NIH]

Thromboses: The formation or presence of a blood clot within a blood vessel during life. [NIH]

Thrombosis: The formation or presence of a blood clot inside a blood vessel. [NIH]

Thymus: An organ that is part of the lymphatic system, in which T lymphocytes grow and

multiply. The thymus is in the chest behind the breastbone. [NIH]

Thyroid: A gland located near the windpipe (trachea) that produces thyroid hormone, which helps regulate growth and metabolism. [NIH]

Tic: An involuntary compulsive, repetitive, stereotyped movement, resembling a purposeful movement because it is coordinated and involves muscles in their normal synergistic relationships; tics usually involve the face and shoulders. [EU]

Ticks: Blood-sucking arachnids of the order Acarina. [NIH]

Tissue: A group or layer of cells that are alike in type and work together to perform a specific function. [NIH]

Tissue Culture: Maintaining or growing of tissue, organ primordia, or the whole or part of an organ in vitro so as to preserve its architecture and/or function (Dorland, 28th ed). Tissue culture includes both organ culture and cell culture. [NIH]

Tolerance: 1. The ability to endure unusually large doses of a drug or toxin. 2. Acquired drug tolerance; a decreasing response to repeated constant doses of a drug or the need for increasing doses to maintain a constant response. [EU]

Tomography: Imaging methods that result in sharp images of objects located on a chosen plane and blurred images located above or below the plane. [NIH]

Tonicity: The normal state of muscular tension. [NIH]

Tooth Preparation: Procedures carried out with regard to the teeth or tooth structures preparatory to specified dental therapeutic and surgical measures. [NIH]

Topical: On the surface of the body. [NIH]

Toxic: Having to do with poison or something harmful to the body. Toxic substances usually cause unwanted side effects. [NIH]

Toxicity: The quality of being poisonous, especially the degree of virulence of a toxic microbe or of a poison. [EU]

Toxicology: The science concerned with the detection, chemical composition, and pharmacologic action of toxic substances or poisons and the treatment and prevention of toxic manifestations. [NIH]

Toxin: A poison; frequently used to refer specifically to a protein produced by some higher plants, certain animals, and pathogenic bacteria, which is highly toxic for other living organisms. Such substances are differentiated from the simple chemical poisons and the vegetable alkaloids by their high molecular weight and antigenicity. [EU]

Transaminase: Aminotransferase (= a subclass of enzymes of the transferase class that catalyse the transfer of an amino group from a donor (generally an amino acid) to an acceptor (generally 2-keto acid). Most of these enzymes are pyridoxal-phosphate-proteins. [EU]

Transcriptase: An enzyme which catalyses the synthesis of a complementary mRNA molecule from a DNA template in the presence of a mixture of the four ribonucleotides (ATP, UTP, GTP and CTP). [NIH]

Transcription Factors: Endogenous substances, usually proteins, which are effective in the initiation, stimulation, or termination of the genetic transcription process. [NIH]

Transduction: The transfer of genes from one cell to another by means of a viral (in the case of bacteria, a bacteriophage) vector or a vector which is similar to a virus particle (pseudovirion). [NIH]

Transfection: The uptake of naked or purified DNA into cells, usually eukaryotic. It is analogous to bacterial transformation. [NIH]

Transfer Factor: Factor derived from leukocyte lysates of immune donors which can transfer both local and systemic cellular immunity to nonimmune recipients. [NIH]

Transferases: Transferases are enzymes transferring a group, for example, the methyl group or a glycosyl group, from one compound (generally regarded as donor) to another compound (generally regarded as acceptor). The classification is based on the scheme "donor:acceptor group transferase". (Enzyme Nomenclature, 1992) EC 2. [NIH]

Transfusion: The infusion of components of blood or whole blood into the bloodstream. The blood may be donated from another person, or it may have been taken from the person earlier and stored until needed. [NIH]

Transgenes: Genes that are introduced into an organism using gene transfer techniques. [NIH]

Transitional cells: Cells that vary in shape depending on whether the tissue is being stretched. The cells may be stretched without breaking apart. They line hollow organs such as the bladder. [NIH]

Translation: The process whereby the genetic information present in the linear sequence of ribonucleotides in mRNA is converted into a corresponding sequence of amino acids in a protein. It occurs on the ribosome and is unidirectional. [NIH]

Translational: The cleavage of signal sequence that directs the passage of the protein through a cell or organelle membrane. [NIH]

Translocation: The movement of material in solution inside the body of the plant. [NIH]

Transplantation: Transference of a tissue or organ, alive or dead, within an individual, between individuals of the same species, or between individuals of different species. [NIH]

Trauma: Any injury, wound, or shock, must frequently physical or structural shock, producing a disturbance. [NIH]

Treatment Outcome: Evaluation undertaken to assess the results or consequences of management and procedures used in combating disease in order to determine the efficacy, effectiveness, safety, practicability, etc., of these interventions in individual cases or series. [NIH]

Tropism: Directed movements and orientations found in plants, such as the turning of the sunflower to face the sun. [NIH]

Tuberculosis: Any of the infectious diseases of man and other animals caused by species of Mycobacterium. [NIH]

Tubulin: A microtubule subunit protein found in large quantities in mammalian brain. It has also been isolated from sperm flagella, cilia, and other sources. Structurally, the protein is a dimer with a molecular weight of approximately 120,000 and a sedimentation coefficient of 5.8S. It binds to colchicine, vincristine, and vinblastine. [NIH]

Tumor marker: A substance sometimes found in an increased amount in the blood, other body fluids, or tissues and which may mean that a certain type of cancer is in the body. Examples of tumor markers include CA 125 (ovarian cancer), CA 15-3 (breast cancer), CEA (ovarian, lung, breast, pancreas, and gastrointestinal tract cancers), and PSA (prostate cancer). Also called biomarker. [NIH]

Tumor Necrosis Factor: Serum glycoprotein produced by activated macrophages and other mammalian mononuclear leukocytes which has necrotizing activity against tumor cell lines and increases ability to reject tumor transplants. It mimics the action of endotoxin but differs from it. It has a molecular weight of less than 70,000 kDa. [NIH]

Tumor suppressor gene: Genes in the body that can suppress or block the development of cancer. [NIH]

Tumour: 1. Swelling, one of the cardinal signs of inflammations; morbid enlargement. 2. A new growth of tissue in which the multiplication of cells is uncontrolled and progressive; called also neoplasm. [EU]

Tunica: A rather vague term to denote the lining coat of hollow organs, tubes, or cavities. [NIH]

Type 2 diabetes: Usually characterized by a gradual onset with minimal or no symptoms of metabolic disturbance and no requirement for exogenous insulin. The peak age of onset is 50 to 60 years. Obesity and possibly a genetic factor are usually present. [NIH]

Tyrosine: A non-essential amino acid. In animals it is synthesized from phenylalanine. It is also the precursor of epinephrine, thyroid hormones, and melanin. [NIH]

Ulcerative colitis: Chronic inflammation of the colon that produces ulcers in its lining. This condition is marked by abdominal pain, cramps, and loose discharges of pus, blood, and mucus from the bowel. [NIH]

Untranslated Regions: The parts of the messenger RNA sequence that do not code for product, i.e. the 5' untranslated regions and 3' untranslated regions. [NIH]

Urethra: The tube through which urine leaves the body. It empties urine from the bladder. [NIH]

Urinary: Having to do with urine or the organs of the body that produce and get rid of urine. [NIH]

Urine: Fluid containing water and waste products. Urine is made by the kidneys, stored in the bladder, and leaves the body through the urethra. [NIH]

Urogenital: Pertaining to the urinary and genital apparatus; genitourinary. [EU]

Uroporphyrinogen Decarboxylase: One of the enzymes active in heme biosynthesis. It catalyzes the decarboxylation of uroporphyrinogen III to coproporphyrinogen III by the conversion of four acetic acid groups to four methyl groups. EC 4.1.1.37. [NIH]

Uterine Contraction: Contraction of the uterine muscle. [NIH]

Uterus: The small, hollow, pear-shaped organ in a woman's pelvis. This is the organ in which a fetus develops. Also called the womb. [NIH]

Vaccination: Administration of vaccines to stimulate the host's immune response. This includes any preparation intended for active immunological prophylaxis. [NIH]

Vaccines: Suspensions of killed or attenuated microorganisms (bacteria, viruses, fungi, protozoa, or rickettsiae), antigenic proteins derived from them, or synthetic constructs, administered for the prevention, amelioration, or treatment of infectious and other diseases. [NIH]

Vaccinia: The cutaneous and occasional systemic reactions associated with vaccination using smallpox (variola) vaccine. [NIH]

Vaccinia Virus: The type species of Orthopoxvirus, related to cowpox virus, but whose true origin is unknown. It has been used as a live vaccine against smallpox. It is also used as a vector for inserting foreign DNA into animals. Rabbitpox virus is a subspecies of vaccinia virus. [NIH]

Vacuoles: Any spaces or cavities within a cell. They may function in digestion, storage, secretion, or excretion. [NIH]

Vagina: The muscular canal extending from the uterus to the exterior of the body. Also called the birth canal. [NIH]

Varicella: Chicken pox. [EU]

Variola: A generalized virus infection with a vesicular rash. [NIH]

Vascular: Pertaining to blood vessels or indicative of a copious blood supply. [EU]

Vasculitis: Inflammation of a blood vessel. [NIH]

VE: The total volume of gas either inspired or expired in one minute. [NIH]

Vector: Plasmid or other self-replicating DNA molecule that transfers DNA between cells in nature or in recombinant DNA technology. [NIH]

Vein: Vessel-carrying blood from various parts of the body to the heart. [NIH]

Venereal: Pertaining or related to or transmitted by sexual contact. [EU]

Venoms: Poisonous animal secretions forming fluid mixtures of many different enzymes, toxins, and other substances. These substances are produced in specialized glands and secreted through specialized delivery systems (nematocysts, spines, fangs, etc.) for disabling prey or predator. [NIH]

Venous: Of or pertaining to the veins. [EU]

Ventricles: Fluid-filled cavities in the heart or brain. [NIH]

Venules: The minute vessels that collect blood from the capillary plexuses and join together to form veins. [NIH]

Vesicular: 1. Composed of or relating to small, saclike bodies. 2. Pertaining to or made up of vesicles on the skin. [EU]

Veterinary Medicine: The medical science concerned with the prevention, diagnosis, and treatment of diseases in animals. [NIH]

Vinblastine: An anticancer drug that belongs to the family of plant drugs called vinca alkaloids. It is a mitotic inhibitor. [NIH]

Vincristine: An anticancer drug that belongs to the family of plant drugs called vinca alkaloids. [NIH]

Viraemia: The presence of virus in blood or blood plasma. [NIH]

Viral: Pertaining to, caused by, or of the nature of virus. [EU]

Viral Hepatitis: Hepatitis caused by a virus. Five different viruses (A, B, C, D, and E) most commonly cause this form of hepatitis. Other rare viruses may also cause hepatitis. [NIH]

Viral Load: The quantity of measurable virus in the blood. Change in viral load, measured in plasma, is used as a surrogate marker in HIV disease progression. [NIH]

Viral Proteins: Proteins found in any species of virus. [NIH]

Viral Regulatory Proteins: Proteins which regulate the rate of transcription of viral structural genes. [NIH]

Viral Structural Proteins: Viral proteins that do not regulate transcription. They are coded by viral structural genes and include nucleocapsid core proteins (gag proteins), enzymes (pol proteins), and membrane components (env proteins). Transcription of viral structural genes is regulated by viral regulatory proteins. [NIH]

Viral vector: A type of virus used in cancer therapy. The virus is changed in the laboratory and cannot cause disease. Viral vectors produce tumor antigens (proteins found on a tumor cell) and can stimulate an antitumor immune response in the body. Viral vectors may also be used to carry genes that can change cancer cells back to normal cells. [NIH]

Viremia: The presence of viruses in the blood. [NIH]

Virion: The infective system of a virus, composed of the viral genome, a protein core, and a protein coat called a capsid, which may be naked or enclosed in a lipoprotein envelope called the peplos. [NIH]

Virulence: The degree of pathogenicity within a group or species of microorganisms or viruses as indicated by case fatality rates and/or the ability of the organism to invade the tissues of the host. [NIH]

Virus: Submicroscopic organism that causes infectious disease. In cancer therapy, some viruses may be made into vaccines that help the body build an immune response to, and kill, tumor cells. [NIH]

Virus Diseases: A general term for diseases produced by viruses. [NIH]

Virus Replication: The process of intracellular viral multiplication, consisting of the synthesis of proteins, nucleic acids, and sometimes lipids, and their assembly into a new infectious particle. [NIH]

Viscera: Any of the large interior organs in any one of the three great cavities of the body, especially in the abdomen. [NIH]

Vitro: Descriptive of an event or enzyme reaction under experimental investigation occurring outside a living organism. Parts of an organism or microorganism are used together with artificial substrates and/or conditions. [NIH]

Vivo: Outside of or removed from the body of a living organism. [NIH]

War: Hostile conflict between organized groups of people. [NIH]

Warts: Benign epidermal proliferations or tumors; some are viral in origin. [NIH]

White blood cell: A type of cell in the immune system that helps the body fight infection and disease. White blood cells include lymphocytes, granulocytes, macrophages, and others. [NIH]

Withdrawal: 1. A pathological retreat from interpersonal contact and social involvement, as may occur in schizophrenia, depression, or schizoid avoidant and schizotypal personality disorders. 2. (DSM III-R) A substance-specific organic brain syndrome that follows the cessation of use or reduction in intake of a psychoactive substance that had been regularly used to induce a state of intoxication. [EU]

Xenograft: The cells of one species transplanted to another species. [NIH]

X-ray: High-energy radiation used in low doses to diagnose diseases and in high doses to treat cancer. [NIH]

Yeasts: A general term for single-celled rounded fungi that reproduce by budding. Brewers' and bakers' yeasts are Saccharomyces cerevisiae; therapeutic dried yeast is dried yeast. [NIH]

Yellow Fever: An acute infectious disease primarily of the tropics, caused by a virus and transmitted to man by mosquitoes of the genera Aedes and Haemagogus. [NIH]

Yellow Fever Virus: The type species of the Flavivirus genus. Principal vector transmission to humans is by Aedes spp. mosquitoes. [NIH]

Zymogen: Inactive form of an enzyme which can then be converted to the active form, usually by excision of a polypeptide, e. g. trypsinogen is the zymogen of trypsin. [NIH]

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