Acute Myeloid Leukemia

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

James N. Parker, M.D.
and Philip M. Parker, Ph.D., Editors

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The collective knowledge generated from academic and applied research summarized in various references has been critical in the creation of this book which is best viewed as a comprehensive compilation and collection of information prepared by various official agencies which produce publications on acute myeloid leukemia. Books in this series draw from various agencies and institutions associated with the United States Department of Health and Human Services, and in particular, the Office of the Secretary of Health and Human Services (OS), the Administration for Children and Families (ACF), the Administration on Aging (AOA), the Agency for Healthcare Research and Quality (AHRQ), the Agency for Toxic Substances and Disease Registry (ATSDR), the Centers for Disease Control and Prevention (CDC), the Food and Drug Administration (FDA), the Healthcare Financing Administration (HCFA), the Health Resources and Services Administration (HRSA), the Indian Health Service (IHS), the institutions of the National Institutes of Health (NIH), the Program Support Center (PSC), and the Substance Abuse and Mental Health Services Administration (SAMHSA). In addition to these sources, information gathered from the National Library of Medicine, the United States Patent Office, the European Union, and their related organizations has been invaluable in the creation of this book. Some of the work represented was financially supported by the Research and Development Committee at INSEAD. This support is gratefully acknowledged. Finally, special thanks are owed to Tiffany Freeman for her excellent editorial support.

About the Editors

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Table of Contents

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 acute myeloid leukemia 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 acute myeloid leukemia, 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 acute myeloid leukemia, 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 acute myeloid leukemia. 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 acute myeloid leukemia, 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 acute myeloid leukemia.

The Editors

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

CHAPTER 1. STUDIES ON ACUTE MYELOID LEUKEMIA

Overview

In this chapter, we will show you how to locate peer-reviewed references and studies on acute myeloid leukemia.

Federally Funded Research on Acute Myeloid Leukemia

The U.S. Government supports a variety of research studies relating to acute myeloid leukemia. 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 acute myeloid leukemia.

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 acute myeloid leukemia. The following is typical of the type of information found when searching the CRISP database for acute myeloid leukemia:

- **Project Title: A NOVEL MASS SPECTROMETRIC ION SOURCE FOR PROTEOMICS**

  Principal Investigator & Institution: Coon, Joshua J.; Chemistry; University of Virginia Charlottesville Box 400195 Charlottesville, Va 22904

  Timing: Fiscal Year 2003; Project Start 30-SEP-2003; Project End 29-SEP-2006

[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).

Summary: (provided by applicant): The overall goals of this research are: (1) to develop a novel high performance liquid chromatography electrospray/ matrix-assisted laser desorption/ionization-mass spectrometry (HPLC-ESI/MALDI-MS) interface to enhance the mass spectrometric identification and sequence analysis of proteins in complex mixtures and (2) to employ this technology to solve problems at the forefront of biological research. The specific aims are to: (1) develop a novel ionization method for mass spectrometry that is capable of increasing proteome coverage, while at the same time providing a more rapid and inexpensive approach for the analysis of proteins in complex mixtures and (2) to apply developed technology to identify proteins that function as diagnostic markers or potential drug targets for acute myeloid leukemias. By operating at atmospheric pressure, the technique will eliminate many of the barriers encountered when combining MALDI with microcapillary HPLC. The method will utilize ESI aerosol droplets to serve as a platform for MALDI ion generation. And unlike any other HPLC-MS approach, this method will capitalize the favorable attributes of both ionization methods simultaneously. This technology will be applied to determine the regulatory pathways involved with the mixed lineage leukemia gene (MLL), which is a common target for chromosome translocation that often results in acute myeloid leukemias. Utilizing HPLC-ESI/MALDI-MS, we propose to identify proteins, induced by the MLL-ENL fusion protein that could function as biomarkers or potential drug targets for treatment of acute myeloid leukemias.

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

- **Project Title: ABERRANT DNA METHYLATION IN ACUTE MYELOID LEUKEMIA**

  Principal Investigator & Institution: Rush, Laura J.; Assistant Professor; Veterinary Biosciences; Ohio State University 1960 Kenny Road Columbus, Oh 43210

  Timing: Fiscal Year 2002; Project Start 01-JUL-2002; Project End 30-JUN-2007

  Summary: (provided by applicant): The overall goal of the K08 award is to permit Laura J. Rush, D.V.M., to devote full-time effort for research training leading to a Ph.D. degree in molecular biology, and for development into an independent scientist for a career in academic biomedical research. Dr. Rush has completed a residency in veterinary and comparative pathology and 3 years of research in the laboratories of Michael A. Caligiuri, M.D., and Christoph Plass, Ph.D., co-sponsors of this award. **Acute myeloid leukemia** (AML) is a heterogeneous disease and the pathogenesis of most types of AML is unknown. The overall hypothesis of this research project is that aberrant DNA methylation in AML is associated with inactivation of genes that are necessary for normal growth, differentiation and/or death of hematopoietic cells, and t h at these epigenetic alterations play a key role in the molecular pathogenesis of AML. The proposed project will focus on fifteen candidate genes that have been identified by genome scanning experiments performed by Dr. Rush using primary AML samples. The goals of the project are to use these 15 genes to: 1) determine the consequences of restoration of gene expression on morphology, differentiation, and growth characteristics in vitro using AML cell lines; 2) investigate the methylation status of the 5' CpG islands by molecular techniques such as bisulfite treatment and methylation-specific in situ hybridization; and 3) correlate aberrant promoter methylation with transcriptional inactivation in AML diagnostic samples. Genes will be prioritized based on expression in normal hematopoietic tissues. The genes will then be transfected into non-expressing AML cell lines to elucidate what effects restoration of expression may have on growth rate, differentiation, b l a s t - colony forming ability, and morphology (Aim 1). Extensive characterization of the methylated 5' regulatory regions of these genes will be performed and results correlated with the presence or absence of the

protein product (Aim 2). Dr. Rush has already developed extensive preliminary data for this project. The cooperative efforts of Dr. Rush, the co-sponsors, and co-investigators in the Division of Human Cancer Genetics, Comprehensive Cancer Center, and the Cancer and Leukemia Group B Tissue Bank will provide a productive environment to complete this significant investigation. The combination of results from studies of primary tumors, in vitro cultures, and mechanistic molecular experiments will contribute to the understanding of the role of aberrant DNA methylation in leukemogenesis.

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

- **Project Title: ABERRANT LARG AND RHOA ACTIVATION IN HUMAN LEUKEMIAS**

  Principal Investigator & Institution: Der, Channing J.; Professor; Pharmacology; University of North Carolina Chapel Hill Aob 104 Airport Drive Cb#1350 Chapel Hill, Nc 27599

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

  Summary: (Adapted from the investigator's abstract) The leukemia-associated Rho guanine nucleotide exchange factor (LARG) was recently identified as a fusion partner of the mixed lineage leukemia (MLL) protein in **acute myeloid leukemia.** LARG is a novel member of the rapidly expanding Dbl family of oncoproteins that promote malignant transformation by activating Ras-related Rho family GTPases. Like other Dbl family proteins, LARG contains a Dbl homology (DH) domain that functions as a guanine nucleotide exchange factor and activator of Rho GTPases. The DH domain is followed by a pleckstrin homology (PH) domain that presumably regulates DH domain function. LARG also contains a regulator of G-protein signaling (RGS) domain, suggesting that it may link G protein-coupled receptor signaling to Rho GTPases. Our preliminary studies determined that LARG is an activator of RhoA and can cause transformation of NIH 3T3 mouse fibroblasts. We have proposed four specific aims to perform detailed structure-function analyses of LARG. Specific aim 1 will determine the roles of the DH and PH domains in mediating LARG activation of RhoA. In particular, whether the PH domain regulates DH domain function in a phosphatidylinositol 3-kinase dependent fashion will be determined. Specific aim 2 will evaluate the role of the RGS domain in linking LARG with G protein coupled receptor signaling. This includes a determination of which heterotrimeric G alpha subunit(s) is regulated by the RGS domain and which G alpha subunit(s) in turn regulates LARG DH domain activation. Specific aim 3 will determine if the tumor-associated MLL-LARG fusion protein is an aberrantly activated form of LARG and can promote growth transformation of epithelial cells and lL-3 independent growth of 32D myeloid cells. Finally, Specific Aim 4 will involve a determination of the crystal structure of the DH/PH domains of LARG complexed with its GTPase target, RhoA, and the determination of the structural basis for DH domain recognition of GTPases. Although the number of Dbl family oncoproteins continue to increase at a rapid pace, to date, LARG is the only functional Dbl protein found to be mutated in human cancer. Our studies will provide a comprehensive, structural, biochemical, and biological analysis of LARG function and assess a role for aberrant LARG activation of RhoA in AML development.

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

- **Project Title: ADOPTIVE CELLULAR THERAPY OF MYELOID LEUKEMIA**

  Principal Investigator & Institution: Molldrem, Jeffrey J.; Chief, Section of Transplant Immunology; University of Texas Md Anderson Can Ctr Cancer Center Houston, Tx 77030

Timing: Fiscal Year 2003; Project Start 05-AUG-2003; Project End 30-APR-2008

Summary: The potent graft versus leukemia effect (GVL) associated with allogeneic bone marrow transplant (BMT) can produce lasting remissions in patients with myeloid leukemia, but the potentially lethal complication of graft versus host disease (GVHD) limits the effectiveness of this treatment. Donor T cells mediate both GVL and GVHD, although the target antigens recognized by these T cells are not known. We hypothesize that GVL would be enhanced and GVHD reduced or eliminated if the target antigens that drove those responses were identified and if T cells with GVL antigen specificity could be isolated and adoptively transferred to leukemia patients. We identified the first human leukemia-associated T cell antigen as PR1, an HLA-A2 restricted nonomer peptide derived from proteinase 3, an aberrantly expressed myeloid-restricted protein in leukemia cells. PR1/HLA-A2 tetramers were used to identify PR1-specific cytotoxic T lymphocytes (CTL) in chronic myeloid leukemia (CML) patients in cytogenetic remission after either interferon or BMT treatment. Using the same deductive strategy that identified PR1, we have shown that CTL with specificity for another antigen, MY4, an HLA-A2 restricted nonomer peptide derived from myeloperoxidase, comprise up to 3% of all CTL in **acute myeloid leukemia** (AML) patients that are in remission after nonmyelcablative stem cell transplant (NST) but are not detectable in patients that relapse. Furthermore, MY4-specific CTL, like PR1-specific CTL, selectively kill AML cells but not healthy bone marrow cells or epithelial cells, a target of GVHD. In this proposal, we will (1) apply this deductive strategy to uncover additional CTL leukemia-associated antigens (LAA), (2) determine whether LAA-specific CTL are present in patients that receive NST and (3) use LAA peptide/MHC tetramers to select and expand CTL for adoptive transfer into recipients of NST to enhance GVL and reduce GVHD.

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

- **Project Title: ARSENIC TRIOXIDE AND ACUTE MYELOID LEUKEMIA**

  Principal Investigator & Institution: Jing, Yongkui; Medicine; Mount Sinai School of Medicine of Nyu of New York University New York, Ny 10029

  Timing: Fiscal Year 2002; Project Start 15-JUL-2002; Project End 30-JUN-2006

  Summary: (provided by applicant): Arsenic trioxide (As2O3) induced complete remission in acute promyelocytic leukemia (APL, AML-M3) patients that relapsed after all trans retinoic acid (tRA) and chemotherapy treatment. Clinical results indicated that the therapeutic effect of As2O3 in APL correlated with the expression of PML-RARalpha , the product of the t(15;17) translocation, and was mediated by apoptosis and non-terminal differentiation induction. We have found that As2O3 degraded PML-RARalpha and allowed RARalpha (from the wild-type allele) to drive APL cell partly differentiation. However, the connection between PML-RARalpha expression on one hand, and apoptosis induction by As2O3 on the other hand, is unclear. We have found that 1) APL cells contained low amounts of glutathione-s-transferase pi (GSTpi), glutathione peroxidase (GPx), catalase and high amounts of myeloperoxidase (MPO); 2) APL cells were highly sensitive to As2O3-induced apoptosis in vitro by a hydrogen peroxide (H2O2) mediated pathway; 3) Ascorbic acid selectively increased As2O3-induced apoptosis in HL-60 cells (which express high amounts of MPO) not in U937 and normal bone progenitors cells (which do not express MPO). We hypothesize that 1) low levels of GSTpi allow As2O3 to inhibit GPx. GPx inhibition in combination with low catalase expression will result in H2O2 accumulation; 2) accumulated H2O2 is converted into reactive oxygen species by MPO, and then trigger apoptosis; 3) PML-RARalpha sensitizes APL cells to As2O3-induced apoptosis by upregulating MPO and/or downregulating GSTpi, catalase and GPx; 4) Ascorbic acid selectively synergizes

As2O3-induced apoptosis in MPO positive AML cells by producing H2O2 and depleting reduced form glutathione (GSH), the substrate of both GSTpi and GPx. The initial aim of the project is to confirm that As2O3 induces apoptosis through H2O2-mediated pathway. This will be tested by comparing H2O2 amount and apoptosis induction in As2O3 treated AML cells. The second aim will determine the central role of GSTpi to control the sensitivity of cells to As2O3-induced H2O2 accumulation and the third aim will examine the functions of MPO in sensitizing As2O3-induced apoptosis. These will be tested by stably transfecting sense or antisense cDNA and using specific inhibitors. The fourth aim will dissect the connection between PML-RARalpha expression and the levels of GSTpi, GPx, catalase and MPO. PML-RARalpha stably transfected cells will be used for this purpose. Our last aim will evaluate the selective apoptosis-induction and the mechanism of As2O3 in combination with ascorbic acid among AML cells with/without expressing MPO in vitro. SCID models bearing AML cells will be used to test the in vivo effect. Successful completion of the proposed studies will not only contribute to elucidation of the mechanism of As2O3-induced remission in APL, but may also provide innovative usage of As2O3 in other forms of AML.

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

- **Project Title: ARSENIC TRIOXIDE AND VITAMIN C IN AML**

  Principal Investigator & Institution: Douer, Dan; Medicine; University of Southern California 2250 Alcazar Street, Csc-219 Los Angeles, Ca 90033

  Timing: Fiscal Year 2004; Project Start 16-APR-2004; Project End 31-MAR-2006

  Summary: (provided by applicant): Arsenic trioxide (As302,) has been shown in clinical trials to have a major therapeutic effect in the **acute myeloid leukemia** (AML) subtype called acute promyeloctyic leukemia (APL). Preliminary in vitro results have suggested that As302 has antineoplastic activity in other tumors including non-APL AML, lymphoid and myeloma cell lines by several mechanisms that overcome cell resistance to chemotherapy. One mechanism is by As3O2 induced apoptosis via intracellular glutathione (GSH) and increased production of reactive oxygen species (ROS). Cancer cells (including AML) with lower glutathione (GSH) levels are more sensitive to As203 induced apoptosis and compounds that decrease intracellular GSH can induce or increase this effect of As203. Several studies have shown that Vitamin C/ascorbic acid (AA) can enhance As302 induced apoptosis in non-AML APL AML, and multiple myeloma cell lines, suggesting that combining As302 with AA may be an effective antineoplastic approach in tumors refractory to chemotherapy. From pilot clinical studies performed so far, this combination could also be less toxic than intensive chemotherapy. Thus, As302 plus AA could also be a safer alternative or possible complementary approach to treat non-APL AML patients who do not want or cannot be treated with intensive conventional chemotherapy. In vitro studies with As302 AA have been done on very few non-APL AML cell lines but samples freshly obtained from many patients. Thus, no patient-to-patient variability is known. We therefore propose to study antineoplastic activity in vitro of As302 by inducing apoptosis and test if such activity could be enhanced by AA on non-APL AML cells freshly obtained from patients. We will also study the mechanism of action focusing on GSH depletion and ROS production. Since phase I studies of combination of As302 plus ascorbic acid have already been found to be safe and well tolerated we will conduct a pilot phase II clinical trial to determine the feasibility, safety and possible efficacy of the combination in patients with non-APL AML who had failed or will not receive chemotherapy. In summary, this combination may have higher benefit/risk ratio in non-APL AML

patients resulting in an overall better outcome with less toxicity than conventional chemotherapy.

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

- **Project Title: ARSENIC TRIOXIDE DOWN-REGULATES STAT3 ACTIVITY IN AML**

  Principal Investigator & Institution: Wetzler, Meir; Roswell Park Cancer Institute Corp Buffalo, Ny 14263

  Timing: Fiscal Year 2003; Project Start 20-MAY-2003; Project End 30-APR-2005

  Summary: (provided by applicant): **Acute myeloid leukemia** (AML) blasts require hematopoietic growth factors for their survival. Growth factors mediate signal transduction through signal transducer and activator of transcription (STAT) proteins. We have demonstrated that STATs are constitutively activated in approximately 50% of AML cases at diagnosis. Blasts with constitutive STAT3 activity have a unique gene profile and are resistant to apoptosis. We have shown that disease-free survival is significantly shorter in patient with, compared to without, constitutive STAT3 activity. Most of the patients in this study were treated with our in-house clinical trial using high-dose cytarabine and idarubicin. Arsenic trioxide (ATO) has growth suppressing activity in acute promyelocytic leukemia. In other types of AML, ATO induces apoptosis, leading to designation of ATO as an orphan drug for AML. However, the precise mechanisms of action of ATO are unknown. We have discovered that ATO down-regulates constitutive STAT3 activity in AML cell lines. We hypothesize that ATO similarly down-regulates STAT3 in blasts from AML patients and thus enhances their sensitivity to undergo apoptosis. We propose to measure the baseline and changes in STAT3 activity in AML blasts during in vivo therapy with ATO. We will accomplish this goal by performing a phase I study of ATO administered over one hour followed by high-dose cytarabine and idarubicin in patients with newly diagnosed AML < 60 years old. We will determine the maximum tolerated dose of ATO in this study and study the effects of in vivo administration of ATO on STAT3 activity, induction of apoptosis and changes in gene expression profiles in AML cells. In addition, we will attempt to identify the mode by which ATO controls the activity of STAT3 and how this effect alters the gene profile patterns and induces apoptosis.

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

- **Project Title: ASSESSMENT OF NOVEL MOLECULAR MARKERS IN AML**

  Principal Investigator & Institution: Gilliland, Gary; Ohio State University 1960 Kenny Road Columbus, Oh 43210

  Timing: Fiscal Year 2003; Project Start 13-MAY-2003; Project End 31-MAR-2009

  Summary: (provided by applicant): Significant advances have been made in the classification and treatment strategies of **acute myeloid leukemia** (AML) based on karyotype (Mrozek et al., 2000). However, it is clear that cytogenetic translocations, inversions and deletions result in changes at the genetic level which in turn are responsible, at least in part, for malignant transformation (Bloomfield and Caligiuri, 2001). Indeed, consistent molecular abnormalities in the absence of an abnormal karyotype are now starting to emerge in AML with some early evidence for an association with clinical outcome. However, some of these prognostic results, including our own, have been inconsistent. This is likely due to inclusion of factors with confounding prognostic significance, such as age, cytogenetics and variations in treatment within each study. In this proposal, we wish to assess the frequency and

predictive value of novel molecular abnormalities in adult AML patients that are enrolled in CALGB treatment protocols (e.g., CALGB 19808 and 10201) and are relatively homogeneous with regard to other important prognostic factors such as cytogenetics, age and treatment. We hypothesize that consistent molecular defects, like certain karyotypes, can be predictive of clinical outcome, can ultimately result in further risk stratification for AML treatment, and can lend insight into treatment approaches for patients with AML. The ultimate goal of the current study is to identify those patients for whom standard therapy will likely result in cure and those patients for whom standard therapy will likely fail, so that therapy can be tailored according to risk, as is currently being done within the CALGB for core binding factor-associated AML. This is a six-year proposal designed to perform definitive analyses on selected pilot studies. The work proposed for CALGB 20202 (which is Project 1 of this LCSC application) follow smaller pilot CALGB studies that are performed and funded by a multitude of investigators using materials from the CALGB Leukemia Tissue Bank (LTB), CALGB 9665. Once these smaller pilot studies are completed and it is determined that they merit further definitive validation, the mechanism described in the current Project 1 will be utilized. As such, this proposal will not attempt to define all the specific analyses to be carried out over the entire six-year funding period, but rather will detail two studies that are currently planned, and provide evidence for the mechanism by which additional studies will be formulated.

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

- **Project Title: BENZODIAZEPINE RECEPTOR AND DRUG RESISTANCE IN AML**

  Principal Investigator & Institution: Banker, Deborah E.; Fred Hutchinson Cancer Research Center Box 19024, 1100 Fairview Ave N Seattle, Wa 98109

  Timing: Fiscal Year 2002; Project Start 01-FEB-2001; Project End 31-JAN-2004

  Summary: We are investigating molecular bases of drug resistance as markers of clinical outcome in **acute myeloid leukemia** (AML) and testing various drug-sensitizing strategies in hopes of improving cure rates for patients with this disease. Relevant chemotherapeutics induce apoptosis and leukemic blasts become drug resistant by downregulating apoptotic responses to these drugs. As a result of anti-apoptotic activities, expression of Bcl-2 family proteins is associated with failure to achieve remission, with short disease-free survival, and with drug-resistant relapse in AML. Bcl-2 proteins are constituents of mitochondrial pore complexes (PTPC) where they block apoptosis by antagonizing mitochondrial pore dissolution that otherwise occurs after lytotoxic treatments. Like Bcl-2, peripheral benzodiazepine receptors (pBzR) reside in PTPC of normal and leukemic blood cells and can protect transfected leukemia cells from apoptosis. However, the association of pBzR expression with clinical outcome has not been directly tested. If high pBzR expression predicts clinical failures in AML, pBzR would be a rational target for molecular anti-leukemia therapies. PK11195 is a high-affinity pBzR antagonist that can block the PTPC protection afforded by Bcl-2 proteins, and can thereby overcome drug resistance. However, whether pBzR or Bcl-2 expresson levels determine the efficacy of PK11195 is unknown. We propose laboratory analyses that will determine the variability of BzR expression in a large number of cell samples collected from AML patients in IRB-approved clinical trials from which complete clinical data is available. We will use standard statistical analyses to determine whether pBzR is an independent prognostic marker in AML. We also propose laboratory analyses of PK11195 efficacy in primary AML cell samples treated with different relevant drugs and in isogenic cell lines over-expressing different anti-apoptotic proteins. NOD/SCID mice will be used as an in vivo model to further test PK11195

efficacy in sensitizing engrafted AML cells. In vitro analyses of normal bone marrow samples and of non-leukemia cells in engrafted mice will examine possible PK11195 toxicities: Data collected in these studies will improve our understanding of the molecular bases of drug resistance in AML. Furthermore, if drug-sensitizing by PK11195 is documented and low toxicity is confirmed in these experiments, novel treatment strategies that include PK11195 will be warranted for AML.

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

- **Project Title: BIOCHEMISTRY OF LEUKEMIA VIRUS CORE BINDING FACTOR**

  Principal Investigator & Institution: Speck, Nancy A.; Professor; Biochemistry; Dartmouth College 11 Rope Ferry Rd. #6210 Hanover, Nh 03755

  Timing: Fiscal Year 2003; Project Start 10-AUG-1993; Project End 30-NOV-2007

  Summary: (provided by applicant): Runx1-CBFbeta is a heterodimeric transcription factor required for the emergence of hematopoietic stem cells in the embryo. During postnatal life mutations in the RUNX1 and CBFB genes in a hematopoietic stem cell or committed progenitor contributes to the formation of human leukemias. The RUNX1 (AML1) gene is disrupted by about a dozen different chromosomal translocations, including the t(8;21), t(12;21), and t(3;21) in acute myeloid and pediatric lymphoblastic leukemias, and in therapy related leukemias and myelodysplasias, respectively. The CBFB gene is rearranged in acute myeloid leukemias by the inv(16). Together, the RUNX1 and CBFB genes are rearranged in approximately one quarter of all acute myeloid and lymphoblastic leukemias. Here we propose to examine the requirement for the Runx1-CBFbeta heterodimer throughout normal hematopoietic development in mice. We will determine whether Runx1-CBFbeta function in a specialized "hemogenic endothelium" is necessary and sufficient in order to produce the first hematopoietic stem cells. We will begin to identify the signals that specify the first hematopoietic stem cells by characterizing the cis-acting sequences that regulate Runx1 expression in the embryo. Finally we will examine the requirement for continued Runx1-CBFbeta function during later stages of postnatal hematopoiesis.

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

- **Project Title: BP1, A HOMEOBOX GENE, IS OVER EXPRESSED IN BREAST CANCER**

  Principal Investigator & Institution: Berg, Patricia E.; Associate Professor; Biochem and Molecular Biology; George Washington University 2121 I St Nw Washington, Dc 20052

  Timing: Fiscal Year 2002; Project Start 01-FEB-2001; Project End 31-JAN-2003

  Summary: We have cloned a potential new human oncogene called BP1 which belongs to an important family of genes referred to as homeobox genes. BP1 was originally identified as a repressor of the human beta globin gene; recent studies in our laboratory demonstrated that BP1 mRNA if over-expressed in 81% of pediatric and 47% of adult acute myeloid leukemias, possibly in early progenitors. In addition, over-expression was observed in 32% of pediatric T-cell acute lymphoblastic leukemia (ALL), although not in pediatric pre-B-ALL. Our molecular studies showed that over-expression of BP1 leads to increased growth and decreased erythroid differentiation in cell lines, indicating a possible mechanism by which BP1 could function as an oncogene. We now have preliminary data implicating BP1 expression in breast cancer. Analysis of seven breast cancer cell lines showed BP1 mRNA levels ranging from barely detectable to highly expressed. Interestingly, cell lines highly expressing BP1 are tumorigenic. BP1 mRNA was highly expressed in 87% of fifteen breast cancer tumors we have examined while, in

contrast, it was expressed at a very low level in one of five normal breast tissue. BP1 expression was seen in 100% of the high grade, estrogen receptor (ER) negative and progesterone receptor (PR) negative cancers but in only 33% of ER positive, PR positive breast cancers. In this proposal we will test the hypothesis that BP1 is a new molecular marker in breast cancer by analyzing its expression in a larger cohort of breast tumors and determining whether a correlation exists between its expression and clinical prognosis. Clinical data is available which will allow us to determine correlations between BP1 expression and node status or tumor grade. Analysis of four specimens to determine whether there is an association between BP1 expression and aberrant expression of any of these genes. This multi-parameter study will therefore determine the clinical relevance of BP1 expression breast cancer.

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

- **Project Title: BROAD SPECTRUM MDR MODULATION IN AML**

  Principal Investigator & Institution: Baer, Maria R.; Roswell Park Cancer Institute Corp Buffalo, Ny 14263

  Timing: Fiscal Year 2003; Project Start 10-FEB-2003; Project End 31-JAN-2005

  Summary: (provided by applicant): Multidrug resistance (MDR) is a major cause of treatment failure in **acute myeloid leukemia** (AML). MDR is frequently associated with energy-dependent drug efflux, and efflux may be blocked by competitive inhibition with non-cytotoxic substrates, termed MDR modulators. Pharmacological modulation of MDRis effective in laboratory models, but clinical application has been disappointing. Trials of pharmacological modulation of MDR in AML have targeted P-glycoprotein (Pgp), the best-characterized MDR-associated transport protein, but additional transport proteins, including muitidrug resistance protein (MRP-1) and breast cancer resistance protein (BCRP), are also likely to contribute to the clinical MDR phenotype. Pharmacological MDR modulation also promotes apoptosis independently of drug efflux, but this effect remains largely unexplored. The overall goal of this proposal is to develop clinical MDR modulation approaches in AML which take into account both the multiple efflux proteins expressed in AML cells and the drug efflux-independent effects of modulators. This requires determining the relevance of expression and function of MRP-1 and BCRP, in addition to Pgp, in AML and the spectrum of activity of available clinically applicable modulators. The studies will utilize the existing Cancer and Leukemia Group B (CALGB) repository of pre-treatment samples from patients > 60 years old with AML occurring de novo and following antecedent myelodysplastic syndromes, a population with a high incidence of clinical MDR, treated on a single protocol, CALGB9720. The specific aims are: 1. To determine the incidence and clinical significance of Pgp, MRP-1 and BCRP expression and function in an AML patient population with a high incidence of clinical drug resistance; 2. To compare the effects of diverse available clinically applicable modulators, including PSC-833, cyclosporine A, Biricodar (VX-710), VX-853, the fumitremorgin C analogue KO143, and the novel taxane-derived agents IDN5109 and tRA96023, on drug retention in AML cells that have been characterized with respect to Pgp, MRP-1 and BCRP expression and function; 3. To compare the drug transport-independent effects of PSC-833, cyclosporineA, biricodar, VX-853, KO143, IDN5109 and tRA96023, onAML cell survival, measured by the apoptotic response. The study is expected to provide essential information for the design of future clinical trials of broad-spectrum MDR modulation in AML and other malignancies.

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

- **Project Title: C/EBPALPHA-MEDIATED THERAPY FOR ACUTE MYELOID LEUKEMIA**

  Principal Investigator & Institution: Radomska, Hanna S.; Beth Israel Deaconess Medical Center St 1005 Boston, Ma 02215

  Timing: Fiscal Year 2002; Project Start 15-SEP-2002; Project End 30-JUN-2005

  Summary: (provided by applicant): The transcription factor C/EBPa is necessary and sufficient for neutrophil differentiation. Expression and/or function of C/EBPalpha were found to be perturbed by various mechanisms in many cases of **acute myeloid leukemia** (AML). Consequently, conditional expression of C/EBPa in leukemic cells re-established their neutrophilic differentiation. This proposal offers novel C/EBPalpha-mediated transcriptional therapies for AML by two approaches. In one, noninvasive delivery of functional C/EBPa protein into nuclei of diseased cells will be utilized. Cell permeable peptides will be fused in frame with C/EBPa protein and expressed in eukaryotic cells. Intracellular protein transport will be achieved through co-culture of the producer cell line with the recipient cells, or by supplying the purified cell permeable C/EBPa proteins into culture media of the recipient cells. Optimized procedure will be applied to primary leukemic bone marrow cells. The expected effects of C/EBPa protein delivery, such as induction of differentiation and apoptosis, will be monitored. In the second approach, a rapid and reproducible cell-based high throughput screen of small molecule chemicals was developed. Briefly, a stable indicator line was made, which harbors luciferase gene under the control of C/EBP-responsive element. Increase in luciferase activity will likely result from augmentation of C/EBPa expression and/or function. Active compounds will be identified and studied to determine the mechanisms of their action. Although this proposal is focused on development of new therapies for AML, successful C/EBPa targeting therapies might be also used for treatment of CML refractory to interferon` or ST1571. The applicant has considerable skills necessary to perform these experiments. Nevertheless, completion of the proposed career development program will further expand her research experience and will enable her to pursue an independent research career.

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

- **Project Title: CELL CYCLE REGULATION AND LEUKEMOGENESIS BY CBFB-SMMHC**

  Principal Investigator & Institution: Friedman, Alan D.; Associate Professor; Oncology; Johns Hopkins University 3400 N Charles St Baltimore, Md 21218

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

  Summary: (provided by applicant): The AML1 or CBFbeta subunits of Core Binding Factor are mutated or translocated in 30% of **acute myeloid leukemia** (AML) cases, Inv(16) encodes CBFbeta-SMMHC, linking CBFbeta to Smooth Muscle Myosin Heavy Chain. Inhibition of CBF blocks differentiation and slows G1 to S cell cycle progression. Mutations, which stimulate G1 may prevent cell cycle inhibition by CBF oncoproteins and potentiate their ability to impede differentiation. Aim 1: To identify the regulatory pathway responsible for variation in AML1 expression during the cell cycle and to determine whether AML1 regulates the cell cycle in normal progenitors. The effect of expressing an siRNA from a retroviral vector in normal or AML1(+/-) progenitors on cell cycle kinetics will be assessed. Endogenous AML1 levels increase sharply as 32D c13 cells enters S, and this is also observed with exogenous AML1, implicating regulated protein stability. The role of cdks and other kinases, protein:protein interaction, and ubiquitination in this process will be determined. Aim 2: To determine whether

CBFbeta-SMMHC and loss of p15INK4b cooperate to induce AML, whether loss of p15 specifically affects myeloid progenitor proliferation, and whether lack of p15 prevents cell cycle inhibition from reduced AML1 activity. CBFbeta-SMMHC cooperates with loss of p16p19 to induce lymphoid leukemias in mice. The p15 promoter is inactivated by methylation in 80% of AMLs, whereas p16p19 abnormalities are rare. Marrow from C57BL/6 p15 (-/-) mice will be transduced with CBFbeta-SMMHC and transplanted. The cell cycle characteristics of myeloid, lymphoid, and erythroid progenitors from p15 (+/+), (+/-), and (-/-) mice will be compared. The effect of AML1 siRNA and of CBFbeta-SMMHC on p15 (-/-) progenitor cell cycle kinetics will be assessed. Aim 3: To determine whether the CBFbeta-SMMHC Assembly Competence Domain is required for transformation, to identify residues critical for ACD function, and to determine their role in corepressor binding. Deletion of a 28 residue segment, the ACD, near the C-terminus of CBFbeta-SMMHC prevents multimerization, inhibition of AML1 transactivation, and inhibition of cell proliferation. We propose to evaluate this deletion in the AML model developed in Aim 2, to identify point mutations in the ACD which prevent multimerization, to assess their effect on AML1 transactivation and on proliferation, and to determine whether they bind mSin3a or HDAC8, as does CBFbeta-SMMHC.

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

- **Project Title: CHEMICAL GENOMICS APPROACH TO LEUKEMIA DIFFERENTIATION**

  Principal Investigator & Institution: Stegmaier, Kimberly; Dana-Farber Cancer Institute 44 Binney St Boston, Ma 02115

  Timing: Fiscal Year 2003; Project Start 01-JUL-2003; Project End 30-JUN-2008

  Summary: (provided by applicant): Long-term survival for patients with **acute myeloid leukemia** (AML) remains poor despite advancement in the understanding of AML pathogenesis. However, the addition of differentiation therapy to chemotherapy regimens for patients with acute promyelocytic leukemia (APL) has greatly increased their survival. Experimental evidence suggests that many myeloid leukemias maintain the molecular machinery for cellular maturation. Unfortunately, there are few known pharmacological triggers of differentiation, and these have shown little efficacy in the treatment of other myeloid malignancies. We hypothesize that alternative differentiating agents exist that may have both therapeutic potential and provide insight into the molecular mechanisms of differentiation. Current methods of performing small molecule library screens are limited. To identify myeloid differentiating agents, we designed a new method of high throughput screening (HTS). In this method, a gene expression pattern served as a surrogate for the differentiated phenotype. A gene expression signature distinguishing primary human AML blasts from normal peripheral blood neutrophils or monocytes was determined using DNA microarrays. These signatures were confirmed to be discriminatory in an HL60 cell line model of hematopoietic differentiation. They were then simplified to a 5 gene multiplexed RT-PCR assay. PCR amplicon was detected with a novel method utilizing mass spectrometry. In this proposed project, we will utilize this screening method both to identify new candidate AML differentiating agents and to optimize exposure conditions for dose response and kinetics. The biological activity of these compounds will be evaluated with multiple assays for proliferation and differentiation, and expression profiling will be used to characterize their molecular consequences. Their activity will then be tested in other myeloid cell lines and in primary patient cells. Using those agents with a confirmed differentiation capacity, we will take a multifaceted approach to

exploring potential mechanisms of myeloid blast differentiation with DNA microarray technology and mechanism-activity relationship testing. These candidate compounds, as well as an improved understanding of myeloid leukemia differentiation, should help direct us to potential therapeutic agents for AML.

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

- **Project Title: CHILDHOOD LEUKEMIA AND ENVIRONMENTAL EXPOSURES**

  Principal Investigator & Institution: Buffler, Patricia A.; Professor of Epidemiology; None; University of California Berkeley Berkeley, Ca 947205940

  Timing: Fiscal Year 2004; Project Start 01-JAN-1999; Project End 31-MAR-2009

  Summary: (provided by applicant): This proposal is designed to identify etiologic associations between environmental exposures and childhood leukemia. The proposal expands an ongoing case control study of children ages 0 to 14 years that has been successfully implemented in 35 Northern and Central California counties. Notably, a high percentage of the subjects (about 40%) are children of Hispanic origin, which is unique in a study of childhood leukemia. Using a design that approximates population based ascertainment, the proposed study will expand the sample size (from 400 to 1148 newly diagnosed incident cases) and refine design and analytical procedures developed during the first five years of "Childhood Leukemia and Environmental Exposures" (R01 ES 09137, 1998-2003). Two matched control subjects for each case will be randomly selected from the statewide birth registry. Increased awareness of the molecular and cytogenetic diversity of leukemia within major subtypes (acute lymphoblastic leukemia and acute myeloid leukemia), and the significance of this diversity for clinical and epidemiologic research, underscore the need to uncover the etiologies of molecularly distinct subgroups of leukemia. We will use molecular-biologic techniques to differentiate leukemia subgroups and to identify the association of environment exposures with each molecular subgroup. For disease classification, biological specimens from case subjects will include pretreatment bone marrow and peripheral blood (collected at the time of diagnosis) and archived newborn blood specimens (collected at birth). To study genetic susceptibility, buccal cell specimens will be collected from cases, controls, and their biological mothers. To measure micronutrients and biomarkers of environmental chemical exposures, peripheral blood specimens will be collected from biological mothers of cases under age 7 and their matched controls. Data on a wide spectrum of environmental exposures (including parental occupational exposures, parental tobacco smoke, pesticides and other chemicals, maternal and child diet, and child immunological factors) will be collected through a detailed in-person interview with a biological parent. This comprehensive information on environmental exposures and genetic characteristics, in conjunction with improved disease classification and stratification by Hispanic status, will provide significant insights into the etiology of childhood leukemia.

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

- **Project Title: CHILDRENS CANCER GROUP**

  Principal Investigator & Institution: Wells, Robert J.; Children's Hospital Med Ctr (Cincinnati) 3333 Burnet Ave Cincinnati, Oh 452293039

  Timing: Fiscal Year 2002; Project Start 01-JUL-1979; Project End 30-NOV-2002

  Summary: The objective of this proposal is to improve the diagnosis, treatment and outcome of children with cancer through participation in protocols designed by the Children's Cancer Group (CCG). We plan to enter eligible patients on CCG protocols,

participate in the development and execution of these protocols, supply materials for and execute biological studies of cancer through CCG, serve as a referral center for other CCG institutions which lack facilities for bone marrow transplantation or for phase I chemotherapy and to perform independent studies which may serve as the basis for future CCG studies. The Children's Hospital Medical Center (CHMC) is the major pediatric medical center in the greater Cincinnati area with a population of 2 million people. CHMC is the only hospital with pediatric inpatient capabilities within a 50 to 75 mile radius of Cincinnati and is one of the largest pediatric medical centers within the United States. There are four medical centers affiliated with CHMC: the University of Kentucky, Lexington, KY; Children's Hospital of Akron, Akron, OH; the Children's Hospital of the Penn State Geiseinger Health System is located in Hershey, PA; and Scottish Rite Children's Hospital, Atlanta, GA. Combined, they serve population areas of another 8 to 10 million people. Together, we have become the largest contributor of patients of CCG studies. With this grant application, we welcome our newest affiliate, Kosair Children's Hospital and the University of Louisville, a long standing CCG member institution which adds another 1 to 1.5 million people to the area we serve. As part of this application the University of Louisville data on past participation is separated from that of the other five institutions. Personnel from CHMC and its affiliates have made many contributions to the administration of the CCG and to its scientific studies. Highlights of this participation include personnel serving as member of the Executive Committee of the CCG, Chair of the AML Strategy Group, and leading study committees. CHMC provides the CCG with one of its oldest and largest pediatric Bone Marrow Transplantation units. This unit has expanded from 8 to 12 beds in the past five years. This unit has been particularly active in transplantation of patients with neuroblastoma, **acute myeloid leukemia** and brain tumors. CHMC is one of the relatively few phase I institutions adding to the CCG's capability to perform these unique and difficult studies. We have also been the leading contributor to cancer biologic studies, a leading contributor to the Human Tumor Tissue Network and have served as a center for pediatric tumor xenografts which allow completion of additional studies of the biology of these tumors.

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

- **Project Title: CHILDRENS CANCER GROUP**

  Principal Investigator & Institution: Neglia, Joseph P.; Pediatrics; University of Minnesota Twin Cities 200 Oak Street Se Minneapolis, Mn 554552070

  Timing: Fiscal Year 2002; Project Start 01-DEC-1976; Project End 30-NOV-2002

  Summary: Dramatic gains have been made in childhood cancer including markedly more effective therapy, insights into the biology of these diseases, a clearer definition of etiologic factors, and a new focus on the outcomes of the survivors of these diseases. These gains have largely been facilitated by the cooperative clinical trials groups. This grant will facilitate the continued involvement of the investigators at the University of Minnesota in the multi-institutional cooperative therapeutic and non- therapeutic studies conducted by the Children's Cancer Group (CCG). Minnesota investigators have been at the forefront of all of these venues over the past grant cycle and are poised to continue this productive relationship into the future. In 1997, the Minnesota consortium registered 162 patients on therapeutic trials (phase I, II, and III) and, in addition, registered patients on almost 100 non-therapeutic (biology, epidemiology) studies. The combination of strong patient accrual, data management, group leadership, and authorship of CCG publications resulted in Minnesota being ranked first among all group institutions in 1995, 1996, and 1997. Minnesota investigators have continued

strong leadership roles in Epidemiology and Cancer Control, Hematopoetic Stem Cell Transplantation, acute lymphoblastic and **acute myeloid leukemia,** biology, and experimental therapeutics. Over the past grant cycle, Minnesota investigators have chaired fourteen group therapeutic or scientific committees and served as vice-chairs on an additional twenty four. Minnesota has consistently led the group in first- authorship of group publications. Institutional research in stem cell transplantation, epidemiology and cancer control, experimental therapeutics, and biology has been applied to group studies and future investigations of all of these areas are under development. This grant requests support for the personnel critical to our future group activities. It will assure continued excellence in data management, allow travel by investigators and other key personnel to group meetings, and supply the funds needed for expenses generated by the accrual of patients to group studies. This funding will assure the continued leadership of Minnesota investigators in all aspects of the Children's Cancer Group over the coming five years.

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

- **Project Title: COOPERATING GENES IN INV(16) ACUTE MYELOID LEUKEMIA**

  Principal Investigator & Institution: Castilla, Lucio; Program in Molecular Medicine; Univ of Massachusetts Med Sch Worcester Office of Research Funding Worcester, Ma 01655

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

  Summary: (provided by applicant): Acute myeloid leukemias (AML) arise from the uncontrolled clonal expansion of hematopoietic progenitor cells. Different subtypes of AML are associated with specific chromosomal translocations. For example, the subtype M4Eo is associated with the chromosome 16 break-and-join inversion of the genes that code for the fusion gene CBFb-MYH11. Within subtypes, additional mutations have also been found in other genes including Ras, p53, and NFl. These mutations could play a role in CBFB-MYH11 mediated AML.We generated the Cbfb-MYH11 knock-in mouse, mimicking the presence of CBFb-MYH11 in human AML-M4Eo. We have shown that Cbfb-MYH11 plays a role in leukemogenesis by blocking hematopoietic differentiation. We hypothesize that AML is the result of a process that involves two-events: 1. The creation of a fusion gene that alters hematopoietic stem cell differentiation and 2. the introduction of one or more other mutations that are associated with apoptosis and/or proliferation. To test these hypotheses we will identify genes that synergize with Cbfb-MYH11 to develop AML. We will first combine retroviral insertional mutagenesis in our knock in mice with inverse PCR to identify genes altered in AML (Aim 1). We will then use retroviral transduction of identified genes and transplantation experiments to test for a transforming role of these genes. As an alternative approach to test our hypotheses, we will use genetic crosses and retroviral transduction experiments to evaluate the functional interactions between Ras associated genes and Cbfb-MYH11 in AML development (Aim 2). Our long-term goals are to understand the genetic mechanisms that determine AML, and to provide targets for the design of improved therapies.

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

- **Project Title: COOPERATING GENETIC EVENTS IN MYELOID LEUKEMIA DEVELOPME**

  Principal Investigator & Institution: Largaespada, David A.; Associate Professor; None; University of Minnesota Twin Cities 200 Oak Street Se Minneapolis, Mn 554552070

  Timing: Fiscal Year 2002; Project Start 01-APR-2000; Project End 31-MAR-2003

Summary: (adapted from the investigator's abstract) Cancer develops as a result of the accumulation of multiple genetic changes in somatic cells, all of which cooperate in inducing the transformed phenotype. In **acute myeloid leukemia** (AML) the number and nature of these "cooperating" oncogenic mutations is most often unknown. The BXH-2 mouse offers a model system ideal for the elucidation of interacting gene mutations. In this model, a Murine Leukemia Virus (MuLV) induces AML by acting as an insertional mutagen. The number of different gene whose expression is altered by proviral insertion and which contribute to leukemia development in BXH-2 mice is likely to be large. At least eight different loci have been identified which are mutated by proviral insertion in multiple BXH-2 leukemias, but none of these loci is involved in more than 15% of the leukemias. Therefore, new and more efficient methods for identifying and cloning these cancer genes have been developed. These techniques include the selection of tumor-specific, somatically-acquired proviruses near CpG islands, which greatly enriches for proviruses near genes involved in leukemogenesis, and the development of a highly efficient inverse PCR-based approach for cloning proviral insertion sites. The combination of these two technologies allows rapid progress toward the goal of understanding the complex network of genes mutated during myeloid leukemia development. These procedures have been used to identify mutations in two genes likely to impact the same cell signaling pathway: Nf1 and Cdc251. It is the goal of this proposal to define the overlap between the oncogenic effects of these mutations and discover other proteins involved in this pathway.

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

- **Project Title: CORE--CLINICAL DATA BASE**

  Principal Investigator & Institution: Khoury, Hanna J.; Washington University Lindell and Skinker Blvd St. Louis, Mo 63130

  Timing: Fiscal Year 2003; Project Start 19-SEP-2003; Project End 31-AUG-2007

  Summary: The identification and enrollment of every adult patient with newly diagnosed and relapsed **acute myeloid leukemia** (AML) and Myelodysplastic Syndrome (MDS) referred to the Siteman Cancer Center and Washington University is vital for the successful establishment of the clinical and genomic database required for this program project. Additionally, clinical, pathologic and therapeutic information are essential for determining the clinical relevance of a newly identified genetic mutation. This Core has therefore two Specific Aims, as follows: 1. We will prospectively identify and enroll every patient with newly diagnosed and relapsed AML and MDS referred to Washington University Siteman Cancer Center into the GAML program project. 2. We will establish a comprehensive clinical leukemia database that will capture epidemiological data, disease-related characteristics, prognostic factors, therapeutic information, and outcomes from all newly diagnosed and relapsed AML and MDS patients referred to Washington University Siteman Cancer Center, Along with genomic data obtained on specimens collected from these patients and stored in the Specimen Acquisition and Expression Profiling Core (Core B), this comprehensive database will provide the Biostatistics Core (Core C) critical elements to test and validate the prognostic significance of a given mutation identified through Project 1.

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

- **Project Title: CORE--CLINICAL RESEARCH SUPPORT COMPONENT**

  Principal Investigator & Institution: Stone, Richard M.; Professor; Dana-Farber Cancer Institute 44 Binney St Boston, Ma 02115

Timing: Fiscal Year 2002; Project Start 01-AUG-2002; Project End 31-MAR-2003

Summary: (provided by applicant): The ultimate objective of the research projects in this program project application is to improve the therapeutic results for patients with myeloid malignancies including **acute myeloid leukemia,** myelodysplastic syndrome, and chronic myeloid leukemia. To achieve this objective, tumor cells and other relevant clinical samples from patients will be collected, catalogued, and distributed to the relevant projects for analysis of the expected therapeutic targets and other molecules that might be important in prognosis or pathophysiology. Secondly, a clinical infrastructure is required to carry out the clinical trials described in Project 5 and additional clinical studies that will emanate from the developmental approaches outlined in Projects 1, 8, 9 & 10. Clinical Research Core resources are required to carry out these functions which extend beyond direct patient care and the clinical laboratory. Without the clinical research support provided in the Core it would be impossible to coordinate the proper collection of multiple research specimens, the adherence to novel complex therapeutic schedules and timely follow-up of patients enrolled on research studies. Also critical to this success of the project is the collaboration of individuals in the Core with the staff from the Biostatistics Core who will provide a quality control system for specimen tracking, computerized data entry, quality of control data and will assist in the design and analysis of the clinical research protocols. The purpose of the Clinical Research Support Core is to provide the following services that will be utilized by all the clinical research studies: 1. To collect research specimens and coordinate patient follow-up at Dana- Farber Partners Cancer Center and collaborating institutions. 2. To act as liaison with outside physicians, hospitals, and biotechnology companies to coordinate the collection of research specimens and follow-up data. 3. To insure that study parameters are followed, ancillary specimens are collected on time and processed properly, confirm eligibility, and patient registration. 4. To insure the accuracy of submitted data from outside sources. 5. To provide data management for the collection of individual patient information.

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

- **Project Title: CYSTATHIONINE B SYNTHASE AND ARA C THERAPY FOR LEUKEMIA**

  Principal Investigator & Institution: Taub, Jeffrey W.; Pediatrics; Wayne State University 656 W. Kirby Detroit, Mi 48202

  Timing: Fiscal Year 2002; Project Start 01-JUL-2001; Project End 30-JUN-2006

  Summary: The goal of this project is to better understand the biology of **acute myeloid leukemia** (AML) in Down syndrome (DS) children related to the association of the chromosome 21-localized gene, cystathionine-beta- synthase (CBS) and response to cytosine arabinoside (ara-C)-based therapy. Childhood AML has the worst prognosis of all major childhood cancers with five year relative survival rates of approximately 37%. In contrast, DS children with AML represent an unique group of leukemia patients in view of having significantly higher event-free survival (EFS) rates (70-100% with relapse rates < 15%) compared to non-DS children when treated with ara-C-based protocols. Thus, identifying the biological basis for the extremely high cure rates of DS AML patients can have very important implications and potentially can lead to improvements in AML therapy for all patients. Our previous results have begun to shed light on the underlying mechanisms responsible for the striking increased EFS in DS AML patients. Our results demonstrating i) significantly increased CBS transcript levels in DS myeloblasts and a correlation with in vitro ara-C sensitivity and ara-CTP generation, ii) dramatic increased in ara-C metabolism to ara-CTP in vitro in leukemia cell lines

transfected with the CBS cDNA, associated with increased in vitro and in vivo ara-C sensitivity, and iii) significant differences in frequency of the 844ins68 CBS gene polymorphism in DS myeloblasts, provide compelling evidence of an integral relationship between CBS gene expression and ara-C metabolism. This mechanisms is likely a major factor that accounts for the increased chemotherapy sensitivity and high cure rates of pediatric DS AML patients. This study will continue to examine over novel hypothesis and laboratory observations which bridge basic research (e.g., understanding the transcriptional regulation of CBS, determining the relation of CBS mutations/polymorphisms and ara-C metabolism) and apply this work to translational studies using clinical leukemia samples. These findings may ultimately be applied clinically to improve the treatment and cure of AML. The specific aims of the study are: 1) To characterize the transcriptional regulation of the CBS gene in leukemia cell lines and clinical leukemia samples; 2) To develop CBS-transfected AML cell models and to determine the mechanistic basis for the effects of CBS on ara-C metabolism and sensitivity; 3) To determine the relationships between CBS gene expression and ara-C sensitivities in patient myeloblasts with wild-type CBS and with the T833C, G919A, 844ins68 CBS gene variants.

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

- **Project Title: DEPSIPEPTIDE: A NOVEL HISTONE DEACYTLASE INHIBITOR IN L**

  Principal Investigator & Institution: Byrd, John C.; Internal Medicine; Ohio State University 1960 Kenny Road Columbus, Oh 43210

  Timing: Fiscal Year 2002; Project Start 07-JUN-2002; Project End 31-MAR-2004

  Summary: (provided by applicant): A fine balance between the enzymatic activity of histone acetyltransferase and histone deacetylase (HDAC) governs levels of posttranslation acetylation of histone lysine residues. Recognition of this regulatory mechanism for gene transcriptional activation is growing. In cell transformation, acetylation is profoundly altered, and accumulation of hypoacetylated histone species occurs. Depsipeptide is a novel HDAC inhibitor completing phase I development in solid tumors; clinical activity has been noted. Studies by our group have shown selective cytotoxicity of depsipeptide toward **acute myeloid leukemia** (AML) and chronic lymphocytic leukemia (CLL) cells compared to normal hematopoetic cells. This cytotoxic effect occurs via an uncommonly exploited pathway of apoptosis, and the effect appears to be related to increasing histone H3 and H4 acetylation. We have demonstrated the ability of depsipeptide to induce gene transcription, cell differentiation, and expression of adhesion/co-stimulatory molecules in human myeloid cell lines and transformed lymphocytes. Synergy with decitabine and up-regulation of the 1D10 antigen was also noted. Based upon these data, we propose to perform the first clinical trial of depsipeptide in leukemia patients in two separate cohorts (AML and CLL). The objectives of our proposal are to 1) determine the safety of administering depsipeptide to two cohorts of leukemia patients (AML and CLL) 2) determine the dose at which a 100 percent increase in the baseline histone acetylation occurs, which will define a minimal effective pharmacologic dose (MEPD) 3) examine the biologic effect of depsipeptide on leukemia cells treated in vivo in patients with CLL and AML with respect to differentiation (AML) and co-stimulatory/adhesion molecule expression(AML and CLL). The specific relationship of these processes to lysine-specific H4 alterations, inhibition of HDAC enzyme activity, and enhanced ex vivo sensitivity to monoclonal antibodies will be assessed. By utilizing this novel study design that target MEPD, we may achieve significant biological effects, while avoiding excess doses of depsipeptide. The clinical and laboratory results of this trial will provide

pharmacokinetic and pharmacodynamic information for additional correlative efforts in both single agent phase II and combination phase I studies.

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

- **Project Title: DEREGULATION OF MYELOPOIESIS BY ZINC FINGER PROTEIN EVI1**

  Principal Investigator & Institution: Perkins, Archibald S.; Associate Professor; Pathology; Yale University 47 College Street, Suite 203 New Haven, Ct 065208047

  Timing: Fiscal Year 2002; Project Start 01-APR-1999; Project End 31-JAN-2004

  Summary: As is the case with most human cancers, **acute myeloid leukemia** (AML) is the result of multiple genetic events, each of which leads to loss of a particular aspect of cellular growth control. Two key aspects of this loss of control involve unrestrained proliferation and a block to differentiation. While circumstantial support for the importance of the latter has come from the analysis of leukemic cell phenotype and the efficacy of differentiation therapy, we do not as yet have a clear molecular understanding of how this is manifested or caused. Evi-1 is a leukemogenic zinc finger transcriptional repressor that is thought to act by interfering with cellular maturation of myeloid cells. We have shown that Evi-1 can blunt the accumulation of C/ebpalpha mRNA during myelopoiesis; C/ebpalpha encodes a transcriptional regulatory protein that is essential for the generation of mature granulocytes. However, transcripts of other myeloid-essential regulatory proteins are unaffected by Evi-1. We therefore hypothesize that EVI-1 affects the expression of a very limited subset of genes that play a regulatory role in myeloid maturation. We further hypothesize that the repression of these genes by EVI-1 results in the block to differentiation. We will approach this by identifying and characterizing differences in transcription between Evi-1-expressing myeloid progenitor cells and control myeloid progenitor cells. The differentially expressed genes may be known or novel, and may be direct or indirect targets of Evi-1 action. Furthermore, we propose to test the importance of these transcriptional differences between Evi-1 expressing cells and control cells by assessing their ability to override the Evi-1 induced interference with myelopoiesis.

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

- **Project Title: DIPHTHERIA FUSION PROTEIN THERAPY OF AML**

  Principal Investigator & Institution: Frankel, Arthur E.; Professor of Medicine; Cancer Biology; Wake Forest University Health Sciences Winston-Salem, Nc 27157

  Timing: Fiscal Year 2002; Project Start 12-DEC-1997; Project End 31-DEC-2006

  Summary: Ten thousand people in the U.S. develop **acute myeloid leukemia** (AML) each year. While many patients achieve remissions with combination chemotherapy, most relapse and die with drug resistant disease. We have produced a diphtheria fusion protein (DT388GMCSF) consisting of the catalytic and translocation domains of diphtheria toxin fused to human granulocyte-macrophage colony- stimulating factor. We initiated a phase I single-arm, inter-patient dose escalation clinical trial of five daily intravenous infusions for patients with relapsed or refractory AML. To date, we have observed dose- related transient elevations in liver enzymes and circulating inflammatory cytokines. Half of the patients were found to have pre- treatment antibodies to DT388GMCSF >2mu g/mL associated with reductions in the peak blood concentrations of DT388GMCSF. Clinical remissions have been observed at the higher dose levels. In the next funding period, we propose to better define the potential role for DT388GMCSF in the care of AML patients. We will complete the on- going phase I

study and expand the cohort of patients at the maximal tolerated dose to better estimate the preliminary response rate and side effects. Further, we propose three areas of laboratory studies to be carried out to facilitate our understanding of the molecular pharmacology of DT388GMCSF in these patients. In Specific Aim 1, the molecular mechanism for the liver damage and cytokine release will be investigated. The amount and types of cytokines released into the blood will be measured. Patient cytokine gene polymorphisms will be determined. A rat model will be used to determine whether the cytokines induce the liver injury. Methods of prevention of the cytokine release and liver injury in the rat will be tested. If successful, such measures may be tested in patients. In Specific Aim 2, anti- DT388GMCSF antibody formation and DT388GMCSF serum levels will continue to be measured and correlated with toxicity and response. In Specific Aim 3, pre-treatment blast proliferation sensitivity to DT388GMCSF will be measured and correlated with clinical response. These studies should lead to the design of pivotal phase II clinical trials to determine the role of this therapeutic in AML management.

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

- **Project Title: DISSECTION OF ONCOGENIC PATHWAYS USING DROSOPHILA**

  Principal Investigator & Institution: Mann, Richard S.; Professor; Biochem & Molecular Biophysics; Columbia University Health Sciences Po Box 49 New York, Ny 10032

  Timing: Fiscal Year 2002; Project Start 01-JUL-2000; Project End 30-JUN-2005

  Summary: (Applicant's Description) The long-term goal of this project is to characterize the genetic pathways controlled by dominantly acting oncogenes. To carry out these studies the model organism, Drosophila melanogaster, will be used because of the ability to carry out powerful genetic screens. The AML-ETO oncogene, which is responsible for a significant fraction of Acute Myeloid Leukemias, will be the focus of these studies. The immediate specific aims are to: 1) characterize the wild type function of the ETO ortholog in Drosophila, called nervy; 2) to characterize the gain-of-function phenotypes that are induced in Drosophila by expressing Nervy and AML-ETO proteins. In addition, the activities of chimeric proteins that are analogous to AML-ETO, but are constructed from the orthologous Drosophila genes, will also be characterized. 3) Once these data are in hand, genetic screens will be conducted in Drosophila to identify genes that interact with Nervy and AML-ETO in vivo. These screens will be identify components of the genetic pathways in which Nervy and AML-ETO function. Once additional components of these pathways have been identified, their relevance to leukemogenesis will be tested. If confirmed, these genes will provide additional targets for the development of anti-cancer drugs and other potentially novel therapies. Moreover, if successful, this approach may set a precedent for analyzing the genetic pathways in which other dominantly acting oncogenes function. The use of Drosophila genetics is proposed to help make connections between genetic functions that cannot be easily identified in mammalian experimental systems.

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

- **Project Title: DNA METHYLATION AS A DIAGNOSTIC MARKER IN AML**

  Principal Investigator & Institution: Plass, Christoph; Associate Professor, Department of Medic; Molecular Virology, Immunology & Medical Genetics; Ohio State University 1960 Kenny Road Columbus, Oh 43210

  Timing: Fiscal Year 2002; Project Start 01-JAN-2002; Project End 31-DEC-2006

Summary: (Provided by applicant): Aberrant DNA methylation in the promoter region of genes is found in a variety of human cancers and is thought to be associated with gene silencing. Restriction Landmark Genomic Scanning (RLGS) is currently the only technique that allows the scanning of thousands of promoter sequences for aberrant DNA methylation in human cancer. Aberrant DNA methylation was recently shown to be a major contributor and an early event in tumorigenesis, especially in the development of **acute myeloid leukemia** (AML). In this application we propose to investigate the role of DNA methylation in AML with special emphasis on clinical correlates. The samples that will be used for this study will come from the CALGB Leukemia Tissue Bank. Our hypothesis is that epigenetic changes (DNA methylation) are equally important as genetic alterations in leukemogenesis but have been underestimated in its extend. Since methylation changes could affect the transcription of genes it is likely that these epigenetic differences contribute to the molecular defects that underlie normal karyotype AML. Subsequently, aberrantly methylated targets can be used to identify novel diagnostic or prognostic biomarkers in AML. To test this hypothesis our specific aims are (1) to study methylation profiles in a subset of normal karyotype AML with blast counts >50 percent. (2) Rigorous statistical and bioinformatical analysis will identify diagnosis and relapse specific methylation events, candidate subclass predicting methylation events and finally methylation targets that correlate with clinical data such as duration of complete remission. (3) A small subset of highly informative methylation targets will be studied in detail by bisulfite sequencing. MS-PCR tests will be developed that allow (4) screening of larger patient samples. Statistical analysis will be performed to determine the value of a methylation event as a diagnostic biomarker or as a marker with predictive value.

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

- **Project Title: EASTERN COOPERATIVE ONCOLOGY GROUP**

  Principal Investigator & Institution: Sparano, Joseph A.; Professor of Medicine; Medicine; Yeshiva University 500 W 185Th St New York, Ny 10033

  Timing: Fiscal Year 2002; Project Start 01-JUN-1978; Project End 30-APR-2004

  Summary: The general aims of the proposal are to expand our knowledge of the biology of cancer, to utilize this knowledge to design new treatments for patients with cancer, to test such new treatments in multi-institutional prospective, randomized clinical trials, and to disseminate the results of such trials through peer review publication in scientific and medical journals, and by presentation at scientific and medical meetings. These aims will be accomplished by 1) accrual of patients to ECOG therapeutic and other trials and by collecting and reporting accurate data from those trials to ECOG in a timely fashion, 2) playing scientific and administrative leadership roles in the Group, 3) conducting local clinical and laboratory pilot studies the results of which may serve as bases for larger ECOG studies, and 4) by utilizing our ECOG participation in the training of oncology fellows and junior faculty in clinical methodology. Our specific aims in the next funding period are to increase accrual to ECOG therapeutic and other trials, and to serve as study chairs of several ECOG trials based entirely or in part on pilot data from this institution, including a study of thrombo-poietin in elderly adults with **acute myeloid leukemia,** a study of theophylline in chronic lymphocytic leukemia, and a study of arsenic trioxide in relapsed acute pro-myelocytic leukemia. In addition, laboratory investigations in colon cancer, cervical cancer and leukemia utilizing fresh and banked samples from patients enrolled on ECOG studies group wide are proposed.

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

- **Project Title: EPIDEMIOLOGY OF DOWN SYNDROME--LEUKEMIA & DOWN SYNDROME**

  Principal Investigator & Institution: Ross, Julie A.; Associate Professor; None; University of Minnesota Twin Cities 200 Oak Street Se Minneapolis, Mn 554552070

  Timing: Fiscal Year 2001; Project Start 25-SEP-1997; Project End 30-JUN-2004

  Summary: The environmental aetiology of Down syndrome (DS) is largely unknown. DS children are at nearly a 20-fold increased risk of developing leukemia compared to children in the general population. Trisomy 21 is also one of the most common acquired cytogenetic abnormalities in childhood leukemia. Thus, constitutional trisomy 21 may represent a first genetic event in the development of leukemia. Since only 1% of DS children ever develop leukemia, subsequent environmental exposures could be responsible for frank leukemia in this population. The proposed investigation will include: 1) children with DS, under the age of 19, diagnosed with acute lymphoblastic leukemia (ALL) or **acute myeloid leukemia** (AML), identified through the CCG; 2) children with DS, under the age of 19, frequency-matched by geographic region, age, and race to DS-leukemia cases; and 3) random-digit dialing (RDD) selected regional controls. The proposed case-control studies will include parental interviews, collection of cytogenetic and morphologic data, and medical record validation. In the first case-control study (DS-leukemia compared to DS without leukemia) the plan is to determine whether children with DS and leukemia share similar risk factors reported to be associated with childhood ALL and/or AML including maternal alcohol exposure during pregnancy, specific parental occupational exposures, maternal history of prior fetal loss, preconceptional and in utero exposure to X rays. Other potential risk factors will also be explored that may be unique to this case group, including childhood medical exposures, frequency of exposure to infections, vitamin supplementation, and maternal diet during pregnancy. In the second case-control study (DS compared to normal population), the plan is to investigate potential risk factors for DS, as epidemiologic investigations concerning the environmental aetiology of DS are limited. Specifically, the following risk factors, based on previous study findings, will be addressed: parental occupations and occupational exposures, parental smoking and alcohol use, prior use of specific contraceptives, family history of Alzheimer's disease, and parental preconception exposure to x-rays. The proposed study would utilize resources available through the CCG and would include: 1) 152 DS-leukemia cases diagnosed over a five-year period from 1/1/97 through 12/31/01 by the CCG; 2) 304 frequency-matched DS controls; and 3) 304 frequency matched RDD controls. It is claimed that each case-control study has adequate statistical power to address the hypotheses being explored.

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

- **Project Title: EXAMINATION OF FLT3 MUTATIONS IN ACUTE MYELOID LEUKEMIA**

  Principal Investigator & Institution: Stirewalt, Derek L.; Fred Hutchinson Cancer Research Center Box 19024, 1100 Fairview Ave N Seattle, Wa 98109

  Timing: Fiscal Year 2002; Project Start 01-JUL-2002; Project End 30-JUN-2007

  Summary: (provided by applicant): Dr. Stirewalt's long-term objective is to develop treatments for patients with AML that will reduce morbidity and improve survival. Over the next five years, Dr. Stirewalt will perform pre- clinical and clinical studies that examine the effects of FLT3 mutations in AML. Specific Aim I: Examine the clinical significance of FLT3 mutations in previously untreated adult patients with AML. The

prognostic significance of FLT3 mutations in adults with AML remains uncertain. Specific Aim I prospectively examines the clinical significance of FLT3 mutations in adult AML patients assigned to SWOG SOl06, a phase III trial consisting of standard dose induction and high dose Ara-C consolidation followed by randomization to observation or Mylotarg. AML patients will be screened for FLT3 mutations using sensitive PCR/SSCP assays. Mutation data will be correlated with clinical outcomes. We hypothesize that FLT3 ITDs will be an independent negative prognostic factor in adult patients with AML. Specific Aim II: Examine the ability of PCR assays for FLT3 ITDs to predict clinical relapse. Approximately 90 percent of FLT3 ITDs occur in patients without a molecular marker for MRD, and we have developed sensitive PCR assays for FLT3 ITDs that may be used as tests for MRD. Specific Aim II examines the ability of MRD assays for FLT3 ITDs to predict clinical relapse in patients on SWOG S0106. The MRD assays for FLT3 ITDs will be performed in all FLT3 positive patients at specific time points during their treatment and results will be correlated with clinical outcomes. We hypothesize that MRD assays using FLT3 ITDs will be predictive of clinical relapse. Specific Aim III: Examine the molecular effectors involved in the activation of mutated FLT3 receptors and develop techniques to counteract the effects of mutated FLT receptors. Data from murine cells with transfected FLT3 ITDs suggest that FLT3 ITDs result in activation of the FL T3 receptors that can be inhibited by nonspecific tyrosine kinase inhibitors. We will transfact genetically engineered FL T3 mutations into murine cells. The effects of these FLT3 mutations on activation of the receptor, MAP kinase, STAT 3&5, c- Jun, and global genetic expression will be examined. We will also determine if antibodies directed against the FL T3 receptor, novel tyrosine kinese inhibitors, and/or non-receptor tyrosine kinase inhibitors can alter the effects of FLT3 mutations. Parallel experiments using patient AML samples with FLT3 ITDs will also be performed. We hypothesize that FLT3 ITDs will premote constitutive activation of the receptor that can be blocked by tyrosine kinase inhibitors. In addition to the research proposal, Dr. Stirewalt has developed an educational program that includes specific training objectives, didactic courses, and formal reviews by his advisors. This educational program will strengthen his background in clinical trial design and methodology. Together, the research proposal and educational program provide Dc Stirewalt with the skills to become an independent clinical investigator.

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

- **Project Title: FLT3 GENOTYPES IN ACUTE MYELOID LEUKEMIA**

  Principal Investigator & Institution: Whitman, Susan P.; Comprehensive Cancer Center; Ohio State University 1960 Kenny Road Columbus, Oh 43210

  Timing: Fiscal Year 2002; Project Start 20-SEP-2002; Project End 31-AUG-2007

  Summary: (provided by applicant): Acute leukemia is a malignancy of the hematopoietic elements that results at least in part from inappropriate activation of tyrosine kinases (TK). The most frequent somatic mutation associated with adult **acute myeloid leukemia** (AML) to date is the internal tandem duplication (ITD) of the FLT3 gene, a member of the Type III PDGF superfamily of receptor TKs. The FLT3 ITD defect results in the constitutive activation of the tyrosine kinase in the absence of ligand binding. Clinical studies thus far, however, have provided contradictory results with regards to presence of FLT3 ITD and prognostic significance of this defect in AML. These inconsistencies may be due to factors known to have confounding prognostic importance, such as varying cytogenetics, age, and treatment regimens. We examined a group of AML patients homogeneous for age, cytogenetics and treatment, and all considered at standard risk for relapse following therapy. We demonstrated three

distinct genotypes among 82 patient samples examined: patients homozygous for the wild type (WT) FLT3 gene; patients heterozygous (FLT3ITD/WT), and patients hemizygous, i.e., FLT3 ITD in the absence of the WT gene, or FLT3ITD/-. Only the latter was a highly significant predictor of profoundly worse prognosis in AML patients compared to the others considered at standard risk. The overall research objective outlined in this proposal is to understand the mechanism by which the hemizygous genotype confers an especially poor prognosis, and to target this molecular defect in vitro and in vivo with a FLT3-specific inhibitor. To accomplish this goal, AIM 1 will investigate if a constitutively active mutant FLT3 in the absence of wild-type FLT3 confers a dominant positive gain-of-function role using in vitro and in vivo models. AIM 2 will assess whether proliferation and survival of FLT3 ITD-positive patient AML cells are selectively inhibited via induction of apoptosis by newly developed FLT3 inhibitor compounds. Funding of this K01 Mentored Minority Career Development Award will provide invaluable training for the applicant in the area of molecular mechanisms of disease, animal models for the study of human leukemia, and molecular targeted approaches to cancer therapy.

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- **Project Title: FUNCTIONAL ANALYSIS OF MLL AND MLL PARTNER FUSIONS**

  Principal Investigator & Institution: Zeleznik-Le, Nancy J.; Assistant Professor; Ob, Gyn, and Reproductive Med; Loyola University Chicago Lewis Towers, 13Th Fl Chicago, Il 60611

  Timing: Fiscal Year 2002; Project Start 10-AUG-1998; Project End 30-JUN-2003

  Summary: (adapted from the investigator's abstract) The overall objective of this proposal is to study the function of the normal MLL protein and of the fusion proteins formed by chromosomal translocations involving MLL that result in leukemia. They will use several approaches to identify downstream target genes of normal MLL and of two MLL fusions, MLL-AF9 and MLL-CBP. AF9 is the most common fusion partner of MLL in **acute myeloid leukemia,** both de novo and secondary to therapy with drugs that target DNA topoisomerase II. CBP is a fusion partner of MLL that has so far been observed only in therapy-related leukemias with one exception. They will identify target genes of normal MLL based on the ability of the MLL protein to bind to a target DNA sequence or structure using immunoprecipitation. From these experiments, they will identify targets of MLL to which it binds either directly or indirectly. They will also define the parameters that control binding, which may include DNA target sequence/structure, interacting proteins, MLL domains involved, and protein modification. Additionally, they will identify genes whose expression is altered by expression of either MLL-AF9 or MLL-CBP fusion proteins using transient or inducible stable expression systems followed by gene expression pattern analysis on a genome-wide scale using cDNA microarrays and oligonucleotide microarray chips. This will identify targets whose altered expression may be important in leukemogenesis, regardless of the mechanism. The direct and the downstream targets will help identify cellular pathways that are deregulated by the fusion proteins and that may be critical for the ultimate leukemia phenotype. Together, the experiments proposed in these two specific aims will provide valuable information regarding the mechanism of MLL and MLL-partner gene function in normal and in leukemic cells.

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

- **Project Title: FUNCTIONAL CHARACTERIZATION OF MLL GENE FUSIONS**

  Principal Investigator & Institution: Caligiuri, Michael A.; Professor and Director; Internal Medicine; Ohio State University 1960 Kenny Road Columbus, Oh 43210

  Timing: Fiscal Year 2002; Project Start 15-DEC-2001; Project End 30-NOV-2006

  Summary: (provided by applicant) This is a revised application. All changes are indicated by, a red line in the right margin. At the molecular level, **acute myeloid leukemia** (AML) is a heterogeneous disease. Recent advances with molecular-based risk stratification of AML and molecular-based therapeutics strongly suggest that elucidation of molecular mechanisms underlying each case of AML will have the greatest impact on increasing the cure rate of this disease. In the majority of AML cases, cytogenetics are either normal or only contain changes in chromosome number that limit one's ability to find leukemogenic gene fusions. Several years ago, our laboratory collaborated to discover a novel molecular defect found in 5-10 percent of AML cases with normal cytogenetics and in the majority of AML cases with trisomy 11 as a sole abnormality. The defect involves a partial tandem duplication (PTD) of the MLL gene, whereby exons 2-6 or 2-8 duplicate in tandem creating a unique self-fusions. Our laboratory has since performed an extensive characterization of the MLL PTD. We hypothesize that the MLL PTD represents a primary molecular defect in myeloid hematopoietic progenitor cells that is responsible, at least in part, for their leukemic transformation. We propose a series of in vitro and in vivo model systems to test this hypothesis and to define the genetic differences that specifically result from the MLL PTD. We have developed a targeting construct to create embryonic stem cells expressing the MLL PTD for in vitro differentiation studies as well as for creation of chimeric and heterozygous mice expressing the MLL PTD. Finally, we have utilized two techniques to study genome-wide genetic and epigenetic changes in leukemic tissue to better understand downstream effector molecules during malignant cell growth, and propose to use these technologies to better understand pathways critical to leukemogenesis in cells harboring the MLL PTD. Ultimately, we believe insights gained by the experiments proposed in this application will further our understanding of leukemogenesis and open up new therapeutic options for this subset of AML patients with a poor prognosis.

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- **Project Title: GENETIC DISSECTION OF DROSOPHILA HEMATOPOIESIS**

  Principal Investigator & Institution: Banerjee, Utpal; Professor & Chair; Molecular, Cellular & Dev Biol; University of California Los Angeles 10920 Wilshire Blvd., Suite 1200 Los Angeles, Ca 90024

  Timing: Fiscal Year 2002; Project Start 10-MAY-2001; Project End 30-APR-2005

  Summary: (Applicant's abstract): The study of lineage specification during hematopoiesis in mammals is important due to its relationship to many blood related disorders including Leukemia. However, many fundamental questions regarding the specification of unique fates remain unresolved. Drosophila has a simple hematopoietic system constituting of cell types that function in innate immunity and phagocytosis. A hierarchy of multiple transcription factors that specify hematopoietic lineage in Drosophila have been identified. The GATA factor Serpent is required for all hematopoiesis. Lozenge, which bears similarity to the **Acute Myeloid Leukemia** protein in humans is required for the development of one blood cell type, the crystal cells in Drosophila. Gcm is required for the development of the plasmatocytes/macrophages. Recently we have established that the Notch receptor and its ligand Serrate are involved in the induction of blood cells in Drosophila. In this proposal, we present a

comprehensive analysis of Drosophila hematopoiesis. The role of Serpent in larval hematopoiesis will be studied; the involvement of the Notch pathway in blood cell development will be fully analyzed. The hematopoietic precursor population will be characterized. A comprehensive genetic study will be performed for a possible role of the many known signal transduction cascades in the process of hematopoieis. Finally, genetic screens will identify genes that are involved in Drosophila hematopoiesis. Given the similarity of the known members of this developmental system with proteins with important function in mammalian hematopoiesis, we expect that many of the new genes identified will have relevance to this important developmental process in mammals.

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- **Project Title: GENETIC DISSECTION OF TUMOR PROGRESSION IN NF-1 AML**

  Principal Investigator & Institution: Brannan, Camilynn I.; Assistant Professor; Molecular Genetics & Microbiol; University of Florida Gainesville, Fl 32611

  Timing: Fiscal Year 2002; Project Start 01-MAY-2002; Project End 30-APR-2006

  Summary: (provided by applicant) Juvenile myelomonocytic leukemia (JMML) is a disease that occurs in young children and is associated with a high mortality rate. In most patients, JMML has a progressive course leading to death by virtue of infection, bleeding or progression to **acute myeloid leukemia** (AML). As it is known that children with Neurofibromatosis type 1 (NF1) have a markedly increased risk of developing JMML, we were able to develop a mouse model of JMML by reconstituting lethally irradiated mice with hematopoetic stem cells homozygous for a loss of function mutation in the Nfl gene. In the course of these experiments, we found that all these genetically identical reconstituted mice developed a JMML-like disorder, but only a subset went on to develop more acute disease. This result strongly suggests that additional genetic lesions are responsible for disease progression. The focus of this proposal is to identify these additional genetic lesions as a means to better understand leukemic progression. Toward this goal, we have placed the Nf1 mutation on the BXH-2 mouse genetic background, a strain known to contain a somatically infectious ecotropic retrovirus. Using this powerful somatic mutagenesis system, we have identified three common ecotropic proviral integration (Epi) sites. We hypothesize that these Epi sites will allow identification of genes that are involved in myeloid tumor progression. We have four specific aims: Specific Aim 1:Determine if viral integration at the Epil site leads to deregulation of the c-myb gene. Specific Aim 2:Characterize the gene interrupted by viral integrations at the Epi2 locus. Specific Aim 3: Characterize the gene interrupted by viral integrations at the Epi3 locus. Specific Aim 4: Identify additional Epi sites involved in tumor progression of JMML.

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

- **Project Title: GENETIC TARGETS OF NITRIC OXIDE IN LEUKEMIA CELLS**

  Principal Investigator & Institution: Shami, Paul J.; Internal Medicine; University of Utah Salt Lake City, Ut 84102

  Timing: Fiscal Year 2002; Project Start 01-JUL-2002; Project End 30-JUN-2005

  Summary: (provided by applicant) Nitric oxide (NO) inhibits growth, induces differentiation and apoptosis in **acute myeloid leukemia** (AML) cells. Using the technique of Representational Difference Analysis of cDNA (RDA), I have identified a novel gene that I have named regulated by nitric oxide or rno. rno is upregulated by NO in AML cells and is expressed exclusively in hematopoietic cells. A cDNA clone of rno was obtained from a normal leukocyte library. The predicted sequence of rno shows that

it belongs to the family of leucine rich repeat proteins and has a high degree of homology to the human ribonuclease inhibitor. PCR and sequencing also revealed that there are at least 3 isoforms of rno. Expression of rno in AML cells inhibits growth, and induces differentiation and apoptosis. The HYPOTHESIS for this proposal is that NO affects the growth and differentiation of AML cells by modulating the expression of specific genes. rno could be involved in mediating the effects of NO on hematopoietic cells. The SPECIFIC AIMS are: AIM 1-Clone and sequence the complete cDNA for rno isoforms: This will be done by screening a cDNA library made from RNA obtained from normal human peripheral blood leukocytes. AIM 2-Demonstrate that rno affects the growth and differentiation of hematopoietic cells. This will be accomplished by transfecting rno into HL-60 cells and determining the effect of rno expression on cell growth and differentiation. The subcellular distribution of rno will be determined using a rno Green Fluorescent Protein fusion gene. rno will be expressed in E. coli and rno protein will be purified to study its effects on RNAse function. Antisera to rno will be raised for further functional studies. rno expression will be determined in normal hematopoietic cells at different stages of differentiation. AIM 3-Identify genes that are modulated by rno: rno will be cloned in an expression vector with an inducible promoter. The vector will be transfected into HL-60 cells. By using cDNA array technology, gene expression differences between rno expressing and non-expressing cells will be identified. AIM 4-Determine the effect of rno expression on AML cell growth in vivo. I will use a human AML xenograft model in NOD/SCID mice. The animals will be inoculated with HL-60 cells that have been transfected with an inducible rno expression vector. Induction of rno expression in the leukemia cells in vivo will be done by treatment of the animals with Tetracycline. The effect of rno expression on leukemia cell growth in vivo will be determined. This work will help understand the mechanism by which NO affects hematopoietic cell growth and differentiation and may constitute the basis for the development of novel strategies for the treatment of AML.

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- **Project Title: GENETICS OF MYELOID NEOPLASIA--MUTAGENESIS IN ZEBRAFISH**

  Principal Investigator & Institution: Look, a Thomas.; Professor of Pediatrics; Dana-Farber Cancer Institute 44 Binney St Boston, Ma 02115

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

  Summary: (provided by applicant): Forward genetic screening in the zebrafish affords an unparalleled opportunity to discover genes required in human blood cell development, and whose alteration can lead to premalignant states or overt leukemia. This proposal tests two linked hypotheses: (i) genome-wide ethylnitrosourea (ENU) mutagenesis screens in the zebrafish can be used to identify dominant and recessive mutations that cause a deficiency or abnormal distribution of circulating granulocytes, implicating genes important in vertebrate myelopoiesis; and (ii) a subset of the genes discovered by this method will have human counterparts that contribute to myelodysplastic syndrome (MDS) and **acute myeloid leukemia** (AML), or to one of the congenital neutropenias that predispose to these malignancies. In preliminary studies, the zebrafish myeloperoxidase (zMpo) gene was cloned to be used in these screens as a granulocyte developmental marker, and its specificity for cells of the granulocytic lineage was demonstrated by RNA in situ analysis during development and adulthood in the fish. Also, detailed morphologic histochemical, electron microscopic and in situ analysis of cells in normal zebrafish blood and kidney (the hematopoietic organ of adult zebrafish) have been performed, and the results will serve as normal benchmarks for the

analysis of myeloid cell development in mutant zebrafish lines recovered during screening. Mutant fish identified by in situ hybridization following ENU mutagenesis (Aim 1) will be analyzed to determine the cell developmental stage at which the mutation occurred (stem vs committed progenitor vs mature) (Aim 2). Next, the chromosomal location of each mutation will be mapped on the zebrafish genome, and examined for synteny with known regions of loss-ofheterozygosity (LOH) in human MDS/AML (Aim 3). Positional cloning (Aim 4) will focus on genes most likely to have deleted or mutated counterparts in these two neoplasias, both characterized by disordered granulocytic development. These zebrafish mutants may also have human homologues among the mutated genes contributing to recessive congenital blood diseases associated with granulocytopenia that can predispose to MDS/AML. Mutant zebrafish lines that harbor mutations in homologues of previously unidentified MDS/AML tumor suppressor genes will also serve as animal models to help identify genes in pathways leading to myeloid malignancy. A long-range goal is to use these models as a starting point for second-generation modifier screens to identify suppressors and enhancers of the genes causing myelopoietic defects, which may then be exploited as targets for therapeutic development. MDS and AML are currently extremely difficult to treat and are generally only curable with myeloablative therapy followed by hematopoietic stem cell transplantation.

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- **Project Title: GENOMICS OF AML ARISING IN SEVERE CONGENITAL NEUTROPENIA: SUSCEPTIBILITY**

  Principal Investigator & Institution: Link, Daniel C.; Associate Professor; Washington University Lindell and Skinker Blvd St. Louis, Mo 63130

  Timing: Fiscal Year 2003; Project Start 19-SEP-2003; Project End 31-AUG-2007

  Summary: Bone marrow failure syndromes are associated with a markedly increased risk of developing **acute myeloid leukemia** (AML). AML arising in the setting of bone marrow failure is associated with distinct clinical and molecular features suggesting that mechanisms of leukemogenesis may be distinct from that seen in de novo AML. As a model for bone marrow failure syndromes in general, mechanisms of leukemogenesis in patients with severe congenital neutropenia (SCN) will be characterized. SCN is an inherited syndrome manifested by severe chronic neutropenia present at birth. Approximately 9% of patients develop AML characterized by a high frequency of chromosome 7 abnormalities. The following specific aims are proposed. Specific Aim 1. We will define the contribution of mutations of the ELA2 gene to the pathogenesis of SCN and development of AML. There is compelling genetic evidence implicating mutations of the ELA2 gene encoding neutrophil elastase (NE) as the cause of most cases of SCN. However, there is no direct proof that expression of mutant NE inhibits granulocytic differentiation, nor have mechanisms of disease pathogenesis been defined. To directly test the hypothesis that ELA2 mutations are causative for SCN, primary hematopoietic progenitor cells will be transduced with lentiviral vectors expressing mutant NE and their effect on granulocytic differentiation characterized. Based on these studies, a mouse model of SCN will be generated, and it will be used to identify mechanisms of disease pathogenesis and leukemogenesis. Specific Aim 2. We will identify genetic progression factors for AML in SCN. Two complementary approaches aimed at gene discovery will be employed. First, the frequency of mutations in candidate genes in samples of AML from patients with SCN will be identified by sequencing. Second, a genome wide scan to identify genetic mutations in any AMLs arising in the mouse model of SCN will be performed, using the expertise and

technology developed in project 2. The validity of gene mutations as bona fide progression factors for leukemia will be tested using mouse models. Gain-of-function mutations of the G-CSFR are acquired in approximately one-third of patients with SCN and are strongly associated with the development of AML. The hypothesis that these G-CSFR mutations are an important genetic progression factor for AML in patients with SCN will be tested.

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

- **Project Title: GENOMICS OF AML: CONTRIBUTION OF CYTOKINE SIGNALLING**

  Principal Investigator & Institution: Tomasson, Michael H.; Washington University Lindell and Skinker Blvd St. Louis, Mo 63130

  Timing: Fiscal Year 2003; Project Start 19-SEP-2003; Project End 31-AUG-2007

  Summary: The long-term objective of this project is to facilitate the development of novel therapeutic targets to improve therapy for patients with AML. The two most common mutations known in patients with **acute myeloid leukemia** (AML) are activating mutations of the gene encoding the FLT3 receptor tyrosine kinase (RTK), and activating mutations in the Ras oncogene (NRAS and KRAS). We hypothesize that every AML tumor harbors at least one mutation in a cytokine signaling gene, and that these mutations activate downstream signaling pathways that contribute to leukemogenesis. To test these hypotheses and to identify novel drug targets, we propose the following Specific Aims: Specific Aim 1: We will comprehensively evaluate AML samples to discover the biological nature and frequency of activating mutations in receptor tyrosine kinase (RTK), non-receptor tyrosine kinase (NRTK), and Ras-MAPK pathway genes. Bone marrow and skin biopsy samples will be obtained following informed consent from patients at our institution with de novo or relapsed AML. In collaboration with the Washington University Genome Sequencing Center (GSC), we will screen for mutations by total exonic resequencing of all known RTK, NRTK and Ras-MAPK pathway genes in patients with AML. Novel mutations identified by the GSC will be characterized using biochemical, cell culture and mouse model assays. Specific Aim 2: We will test potential cooperative functional interactions between mutations in cytokine signaling pathway genes with transcription factor mutations in mice. A mouse model of AML has been developed by coexpressing the RTK fusion oncogene TEL-PDGFRB with the AML1-ETO transcription factor oncogene, providing proof of principle that cytokine signaling pathway mutations provide a critical function in the development of leukemia. Signaling mutants of TEL-PDGFRB and gain-of-function mutations of the AKT/PKB, NRas and STAT5a genes will be coexpressed with AML1-ETO or PML-RARA in primary murine hematopoietic cells to identify signaling pathways that cooperate to cause acute leukemia in mice. Lastly, novel mutations in cytokine signaling genes identified in Aim 1 will also be tested for their ability to induce leukemia via cooperation with transcription factor fusion oncogenes in vivo.

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

- **Project Title: IMMUNE RESPONSES TO ACUTE MYELOID LEUKEMIA CELLS**

  Principal Investigator & Institution: Stripecke, Renata; Institute for Genetic Medicine; University of Southern California 2250 Alcazar Street, Csc-219 Los Angeles, Ca 90033

  Timing: Fiscal Year 2002; Project Start 07-SEP-2000; Project End 30-JUN-2003

  Summary: Research Project: We propose to genetically modify AML cells to produce molecules that promote potent immune-stimulation. HIV-derived lentiviral vectors can

efficiently transduce primary AML cells and promote stable and high levels of transgene expression. Novel self-inactivating (SIN) vectors have been recently developed, providing additional biosafety to the lentiviral vector system. We will employ the SIN-lentivirus to deliver genes encoding immunomodulators that function in various pathways of immune-stimulation (CD80, CD70, GM-CSF, CD40L, FLT3L, IL-4). AML cells expressing a single or a combination of immunomodulators will be evaluated by in vitro assays on their ability to promote T-cell, B-cell, dendritic cell mediated immune responses. The biosafety of the lentiviral vectors will be evaluated by in vitro culture systems. Ultimately, we propose to develop a clinical protocol for immunization of AML patients with irradiated, lentivirus transduced cell vaccines. Long-term, disease-free survival is currently achieved in only approximately 30 percent of patients with AML. Major improvement in long-term survival for AML patients could possibly be achieved by active immunotherapy during remission to eradicate minimal residual disease, thus lowering the risks of relapse.

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- **Project Title: IMPLICATIONS OF RETINOID-INDUCED CD38 ANTIGEN EXPRESSION**

  Principal Investigator & Institution: Mehta, Kapil; Associate Professor; Bioimmunotherapy; University of Texas Md Anderson Can Ctr Cancer Center Houston, Tx 77030

  Timing: Fiscal Year 2003; Project Start 01-MAY-2003; Project End 30-APR-2007

  Summary: (provided by applicant): AII-trans retinoic acid (RA) represents a major advance that has made acute promyelocytic leukemia (APL) the most curable subtype of **acute myeloid leukemia** in adults. Although, RA's overall toxicity is considerably less compared to the standard toxic chemotherapy, its use has been associated with the development of a potentially fatal condition called, RA syndrome. The only drug available for preventing RA syndrome is the high dose of dexamethasone, even though its mechanism of action is not understood. The pathogenesis of RA syndrome and management remains to be the challenge for the present. The syndrome is typical of APL patients; it neither occurs in individuals taking RA for other reasons nor the APL patients treated with chemotherapy alone develop this condition. More specifically, the syndrome has not been observed in APL patients receiving RA during complete remission. Based on these observations, it is postulated that RA syndrome may represents a secondary event related to the aberrant interaction between differentiating myeloid cells and host tissues. Based on our initial observations that: a) RA-is a potent inducer of cell-surface CD38 antigen expression in APL cells; b) CD38 antigen can serve as a receptor and its ligation can induce potent growth-stimulatory and inflammatory signals; and c) human lung endothelial cells express a cell-surface protein that can serve as a putative CD38 ligand; we propose that RA-induced CD38 antigen may play a central role in the development of RA syndrome pathogenesis. Thus, RA-induced CD38 antigen may result in an increased adherence between CD38-positive maturing APL cells and the endothelium of lung capillaries. This initial step may generate the congestive clinical picture and induce (or may determine) an uncontrolled cytokine release. The studies proposed in this grant application will address in depth the involvement of CD38 antigen in promoting the adhesion of RA-induced APL cells to lung endothelial cells and consequence and contribution of such interaction in the development of RA syndrome. By accomplishing the stated aims, we hope to define the molecular mechanisms involved in the pathogenesis of RA syndrome, the knowledge that will help design better approaches to control this potentially fatal condition.

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- **Project Title: IN VIVO ANALYSIS OF A TRANSCRIPTIONAL COACTIVATOR DOMAIN**

  Principal Investigator & Institution: Brindle, Paul K.; Assistant Member; St. Jude Children's Research Hospital Memphis, Tn 381052794

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

  Summary: (Scanned from the applicant's abstract) Many developmental and physiological processes involve the regulation of gene expression by specific DNA-binding transcription factors (TFs). The cAMP- and calcium-responsive factor CREB, and the hematopoietic cell-determining factor c-Myb, bind to their respective target promoters and enhancers, and stimulate transcription by binding the transcriptional coactivators CREB-binding protein (CBP) and its paralog p300. In humans, CBP mutations are associated with **acute myeloid leukemia** and Rubinstein-Taybi Syndrome (RTS is characterized by mental retardation, craniofacial defects, broad big toes and thumbs, and an abnormal incidence of neoplasms). CBP and p300 have at least four distinct TF-binding domains that act as nuclear foci for different intracellular signaling pathways. One of these domains, KIX, has been extensively studied in vitro as a convergence point for cAMP- and calcium-signals through CREB, but also as a mediator of c-Myb tissue specific activity. In order to understand how TFs interact with transcriptional co-activators to drive tissue- and signal-specific gene expression in mammals, the CBP and p300 KIX domains will be tested in vivo by introducing genes with targeted MX mutations into mice by homologous recombination. Mutating KIX in CBP results in a hypomorphic protein that has characteristics unique from those of wild-type CBP in transcription assays. These mutant mice will be used to elucidate CBP- and p300-KIX-dependent functions in development, physiology and gene expression in vivo. Embryonic fibroblast cells derived form KIX mutant mice will be used to study MX functions using transcription assays in vitro, to map CBP/p300 domains necessary and sufficient to rescue KIX-dependent TF activity, and to biochemically characterize the mutant co-activators. If successful, these studies will develop new model systems for studying in vitro and in vivo the roles of CBP and p300 in tissue-specific and signal-dependent transcription. Additional insight will be gained about the role of the MX domain in previously described target tissues of the CREB and Myb families of proteins, including the brain, blood, mammary gland, and testes. KIX mutant mice will also be valuable models for studying the roles of these co-activators in physiological processes relevant to human health such as memory, immunity, reproduction, growth, aging, and metabolism.

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- **Project Title: INVOLVEMENT OF JAK/STAT PATHWAY IN IL-17R SIGNALING**

  Principal Investigator & Institution: Adunyah, Samuel E.; Assistant Professor and Chairman; Biochemistry; Meharry Medical College 1005-D B Todd Blvd Nashville, Tn 37208

  Timing: Fiscal Year 2001; Project Start 15-SEP-1999; Project End 31-AUG-2004

  Summary: Human Interleukin-17 (hIL-17) is novel a cytokine produced by activated T cells. HIL-17 induces T cell proliferation and stimulates production of cytokines (IL-1, IL-6, TNF and IL-8), colony stimulating factors (GM- CSF and G-CSF) and ICAM in fibroblasts. HIL-17 stimulates U937 leukemia cell proliferation. It is considered to be a vehicle for fine tuning hematopoiesis. Based on its ability to stimulate IL-8 production,

hIL-17 is considered to play a role in pro-inflammatory response. Because of its ability to regulate hematopoiesis, it is predicted to emerge as a future clinical tool for the management of **acute myeloid leukemia,** erythroleukemia, immune disorders (T and B cell malignancies) and bone marrow suppression. In spite of its elaborate biologic functions, information on its mechanisms of action is lacking. Therefore, the question of how this cytokine transduces it signal to the nucleus leading to growth regulation and cytokine production awaits to be addressed. The overall goal of this investigation is to elucidate the mechanisms of action of this novel cytokine. Our immediate specific aims are (1) determination of whether Tyk2, STAT4, STAT5 and STAT6 are activated by hIL-17, (2) determination of whether Tyk2, STAT4, STAT5 and STAT6 are activated by hIL-17, (2) determination of whether activation of specific Jak/STAT proteins by hIL-17 correlates with the DNA binding of specific STAT complexes and cytokine gene expression, and (3) determination of whether activation of specific Jak/STAT protein by hIL-17 correlates with the status of cell proliferation/differentiation and cytokine production. By conducting these studies, we will make significant contributions towards the understanding of the mechanisms of action of hIL-17. The outcome would be beneficial to physicians and immunologists for future design of strategies on applications of hIL-17 for the management of diseases of abnormal hematopoiesis and immune system. By employing various techniques including antisense oligonucleotide therapy, Western/Northern blot hybridization, ELISA, immunoprecipitation, kinase assays, PCR and flow cytometry, we can accomplish these aims within three years.

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- **Project Title: INVOLVEMENT OF RUNX1 IN MEGAKARYOCYTIC DIFFERENTIATION**

  Principal Investigator & Institution: Goldfarb, Adam N.; Associate Professor; Pathology; University of Virginia Charlottesville Box 400195 Charlottesville, Va 22904

  Timing: Fiscal Year 2003; Project Start 23-APR-2003; Project End 31-MAR-2008

  Summary: (provided by applicant): Understanding the transcriptional regulation of megakaryocytic lineage commitment will provide guidance in designing treatments for many bone marrow disorders associated with thrombocytopenia. We have identified the myeloid transcription factor RUNX1 as a protein upregulated early in megakaryocytic differentiation and downregulated early in erythroid differentiation. This expression pattern is unique in that virtually all other megakaryocytic transcription factors, such as GATA-1, FOG-1, NF-E2, and SCL/tal, display shared expression in both megakaryocytic and erythroid lineages. The restricted coexpression of RUNX1 and GATA-1 in megakaryocytes led us to discover that these factors strongly cooperate in the activation of a megakaryocytic promoter. This cooperation depends on RUNX1 binding sites present in the promoter and on the RUNX1 cofactor CBFbeta. Co-immunoprecipitation assays demonstrate physical association of RUNX1/CBFbeta with GATA. This novel functional and physical association correlates with the recent clinical implications of both the GATA-1 and RUNX1 genes in hereditary syndromes with thrombocytopenia. A dominant-negative variant of RUNX1 consists of a fusion with the ETO transcriptional repressor that results from the t(8;21) chromosomal abnormality frequently found in **acute myeloid leukemia.** We have found that the RUNX1-ETO oncoprotein, in contrast to wild type RUNX1, potently inhibits GATA-1 activation of a megakaryocytic promoter. In addition, RUNX1-ETO demonstrates physical interaction with GATA-1. Thus, one of the oncogenic effects of RUNX1-ETO may consist of blocking GATA driven hematopoietic differentiation. The major aims of this project are: 1) Delineation of the developmental consequences and molecular mechanisms of

RUNX1 synergy with GATA-1 in megakaryopoiesis; 2) Determination of the developmental consequences and molecular mechanisms of RUNX1-ETO inhibition of GATA factors.

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- **Project Title: MECHANISMS OF G-CSF RECEPTOR MEDIATED DIFFERENTIATION**

  Principal Investigator & Institution: Tweardy, David J.; Professor; Medicine; Baylor College of Medicine 1 Baylor Plaza Houston, Tx 77030

  Timing: Fiscal Year 2002; Project Start 01-MAY-1996; Project End 30-JUN-2007

  Summary: (provided by applicant): G-CSF is the cytokine most critical for driving neutrophil differentiation The majority of **acute myeloid leukemia** (AML) cases arise from this lineage. However, AML cells, unlike their normal myeloid counterparts, respond aberrantly to G-CSF by proliferating without differentiating. The basis for this aberrant response is unknown. The hypo as pursued during the previous funding period was that signaling downstream of the G-CSFR was aberrant in AML cells. G-CSFR was immunoprecipitated in human neutrophils (PMN) after ligand activation. Three phosphoproteins were identified that were activated and associated with the G-CSFR, Lyn, Syk and Stat3. In contrast to Lyn and Syk, Stat3 proved to be required for G-CSF-mediated neutrophilic differentiation in the murine myeloblast cell line model, 32DcI3. However, which Stat3 isoform is responsible for G-CSF-mediated neutrophil differentiation, Stat3a or Stat3beta (or both) has not been determined. Human CD34+cord blood mononuclear cells express predominantly Stat3a while mature PMN express predominantly Stat3beta. Stat3a but not Stat3beta is down regulated midway through the process of G-CSF-induced neutrophilic differentiation of CD34+ cord blood cells and 32Dcl3 cells resulting in a ratio similar to that observed in mature PMN. In contrast, the ratio of Stat3a to Stat3beta protein in AML cell lines is high and remains unchanged following prolonged G-CSF exposure (14 days). Most intriguingly, constitutive overexpression of Stat3a in 32Dc13 cells was shown to inhibit G-CSF-induced neutrophilic differentiation. In this competitive renewal application we will pursue the central hypothesis that the balance of Stat3a to Stat3bet activated by G-CSF in myeloid cells dictates the gene expression profile and, as a consequence, the ability of these cells to differentiate in response to this critical granulopoietin. The Specific Aims of this proposal are: 1) to determine the effects of genetically altered Stat3a to Stat3B ratios on neutrophil differentiation and cell proliferation in 32Dcl3 cells using stable transfection of Stat3 isoforms in an inducible promoter system, 2) to determine the effects of genetically altered Stat3a to Stat3B ratios on neutrophil differentiation and myeloid progenitor cell expansion in vivo by generating transgenic mice deficient in each isoform and 3) to determine the effects of altered Stat3a and Stat3B ratios on gene expression in 32Dcl3 and in hematopoietic cells from Stat3 isoform deficient mice by directed examination of 13 known Stat3 gene targets and using cDNA microarray analysis. The goal of this proposal is to identify gene targets downstream of Stat3B and Stat3a that promote or delay G-CSF-mediated neutrophil differentiation, respectively. Identification of these target genes and how their regulation is altered in AML cells may account for the aberrant response of these cells to G-CSF.

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- **Project Title: MECHANISMS OF HOX GENE REGULATION BY MLL**

  Principal Investigator & Institution: Hess, Jay L.; Associate Professor; Pathology and Lab Medicine; University of Pennsylvania 3451 Walnut Street Philadelphia, Pa 19104

Timing: Fiscal Year 2003; Project Start 01-JUL-1998; Project End 30-JUN-2008

Summary: (provided by applicant): Rearrangements of the mixed lineage leukemia gene (MLL), the human homologue of the Drosophila gene Trithorax (trx), are associated with aggressive lymphoid and myeloid leukemias in both children and adults. Fusion of MLL to one of over 25 different translocation partners converts it into a leukemogenic oncoprotein. In addition internal tandem duplications of MLL occur in about 10% of acute myeloid leukemias with normal cytogenetics and are associated with a poor prognosis. A rapidly growing body of evidence suggests that MLL fusion proteins transform via increased expression of Hox genes, including Hox a9, which in cooperation with the Hox cofactor Meis1, promote leukemogenesis. Our studies of wild-type MLL indicate that it is a histone methyltransferase that dynamically regulates Hox gene expression. MLL binds directly to Hox promoters resulting in both histone acetylation and histone H3 lysine 4 methylation. MLL fusion proteins also upregulate expression of Hox genes and Meis1, which is likely the mechanism by which these proteins cause leukemia. These findings provide a strong rationale and experimental framework for defining how leukemogenic forms of MLL modify the histone code to deregulate Hox gene expression. In SA#1 we will define how wild-type MLL fusion modifies the "histone code" at target Hox genes, and determine how this code is differentially altered by MLL fusion proteins in hematopoietic cells. In SA#2 we examine how targeting of MLL to Hox promoters results in increased histone acetylation. Specifically we will determine if MLL affects recruitment of histone deacetylase containing corepressor complexes to target promoters and explore the role of a highly conserved domain of MLL in this process. In SA#3 we will examine whether coregulator recruitment changes during the downregulation of Hox a9 expression that occurs during myeloid differentiation and how this process may be perturbed by leukemogenic forms of MLL. These experiments will provide fundamental insights into mechanisms of transcriptional regulation by MLL and may facilitate the development of targeted therapies for acute leukemias with MLL rearrangements.

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- **Project Title: MOLECULAR BASIS OF SIGNALING BY THE CABL PROTO-ONCOGENE**

  Principal Investigator & Institution: Pendergast, Ann M.; Associate Professor; Pharmacology and Cancer Biology; Duke University Durham, Nc 27710

  Timing: Fiscal Year 2002; Project Start 15-MAY-1996; Project End 30-JUN-2005

  Summary: (Adapted from the investigator's abstract) The long term objective of this research is to elucidate the biological role of the c-Able proto-oncogene. Mutant forms of c-Abl are associated with the development of murine, feline and human leukemias. Elucidation of a biological role for the c-Abl tyrosine kinase has been hampered for nearly 20 years due to a lack of knowledge regarding the signals that lead to c-Abl activation and definition of the physiological relevance of the activated c-Abl tyrosine kinase in mammalian cells. A seminal discovery in the PI's laboratory was the finding that c-Abl is activated in response to stimulation of growth factor receptor tyrosine kinases and Src family kinases. Significantly, we have shown that c-Abl plays a functional role in the reorganization of the actin cytoskeleton in response to growth factors. Also, we have demonstrated that engagement of the B cell receptor results in an increase in the levels of cytosolic c-Abl tyrosine kinase activity and binding of the c-Abl SH2 domain to the surface protein CD19 in B cells. Studies in the PI's laboratory have uncovered a family of Abl-interacting (Abi) proteins that bind functionally to c-Abl in vivo and may provide insights into the biological role(s) of the Abl tyrosine kinases. The

Abi proteins have been recently implicated in oncogenesis. Abi proteins are targeted for destruction by oncogenic forms of the Abl and Src tyrosine kinases. Moreover, Abi1 is translocated to the MLL gene in **acute myeloid leukemia** with the t(10;11) chromosomal translocation. Recently, Abi proteins have been implicated in the transduction of signals from Ras to Rac. Like c-Abl, the Abi proteins have been shown to be required for reorganization of the cytoskeleton in response to growth factors. The specific aims of this proposal are: 1) to define the pathway whereby c-Abl is activated by growth factor receptors, and to elucidate the role of c-Abl in growth factor and Src signaling; and 2) to identify signaling proteins that link c-Abl to cytoskeletal processes such as cell adhesion, spreading and migration. Primarily, the PI will examine the role of the Abi adaptorss in these processes. The availability of mice with targeted deletions of abi-1 and abi-2 will greatly facilitate the elucidation of the functional roles of these adaptors in normal and transformed cells. Deregulation of the c-Abl kinase downstream of constitutively activated forms of receptor kinases, Src family kinases and by mutated Abi proteins may play a role in the development of multiple human cancers. Results from the aims proposed will shed light on the biological role(s) of c-Abl and allow for a better understanding of the pathophysiological consequences of deregulated Abl tyrosine kinase activity in human cancers.

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- **Project Title: MOLECULAR BIOLOGY OF MYELOID DIFFERENTIATION**

  Principal Investigator & Institution: Tenen, Daniel G.; Associate Professor of Medicine; Beth Israel Deaconess Medical Center St 1005 Boston, Ma 02215

  Timing: Fiscal Year 2004; Project Start 01-JAN-1986; Project End 31-DEC-2008

  Summary: (provided by applicant): The molecular controls governing commitment of hematopoietic stem cells to specific lineages have still not been fully elucidated. The importance of understanding such controls is underscored by the fact that a block in differentiation is a hallmark of acute leukemias. **Acute myeloid leukemia** (AML), involving the precursors of myeloid cells (granulocytes and monocytes/macrophages), accounts for over 90 percent of acute leukemias in adults. In this application, I propose to continue our study of the molecular basis of differentiation of myeloid cells, employing a detailed analysis of the transcription factor PU.1, which regulates nearly every myeloid gene, and is absolutely required for normal myeloid development. PU.1 is expressed in stem cells and upregulated early during myeloid and lymphoid commitment. The importance of understanding how PU.1 is regulated is underscored by studies indicating that altered expression of PU. 1 can induce changes in hematopoietic lineage development, and in some experimental cases misexpression leads to leukemia. Thus, the overall goal of this continuation proposal is to continue our studies of how PU.1 is regulated, and what its function is in adult hematopoiesis. These studies will further our understanding of (1) commitment of normal hematopoietic precursors to the myeloid lineage; and (2) the block in normal myeloid maturation from blasts to mature myeloid cells in AML. Therefore, the Specific Aims are: (1)To determine how PU.1 expression is regulated in hematopoietic cells, using transgenic and knockout studies; (2) To determine the role of PU.1 in adult hematopoiesis by studying a conditional knockout model; and (3) To determine whether different levels of PU. 1 expression play a role in directing hematopoietic lineage determination and development.

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- **Project Title: MOLECULAR CHARACTERIZATION OF ACUTE MYELOID LEUKEMIA**

  Principal Investigator & Institution: Weissman, Irving L.; Professor; Pathology; Stanford University Stanford, Ca 94305

  Timing: Fiscal Year 2002; Project Start 01-JUL-2000; Project End 30-JUN-2005

  Summary: (Adapted from the investigator's abstract) The myeloid leukemias are a major cause of human mortality and morbidity. Since molecular defects in cancer cells often involve genes that regulate programmed cell death (PCD), Dr. Weissman has created transgenic mice that constitutively express the human anti-apoptosis gene bcl-2 in monocytes, neutrophils, and their common progenitors by using the hMRP8 promoter. hMRP8bcl-2 mice develop a massive buildup of stem cells, myelomonocytic progenitors, and monocytes in a syndrome that mimics human chronic myelomonocytic leukemia (CMML). Despite the development of CMML, hMRP8bcl-2 mice rarely progress to **acute myeloid leukemia** (AML). Primitive myeloid blast cells from hMRP8bcl-2 mice express the Fas receptor and, despite overexpression of Bcl-2, are induced to die by Fas ligation. To provide a further block in PCD in the myeloid lineage, he crossed hMRP8bcl-2 mice with Fas-deficient Fas lpr/lpr mice. Fifteen percent of Fas lpr/lpr hMRP8bcl-2 mice developed fatal AML-M2 by 8 weeks of age, but rarely thereafter. This grant will test whether immune surveillance limits AML development past 8 weeks, and whether additional mutations in known or novel proto-oncogenes collaborate with "deathless" myeloid precursors to cause AML. Transduction of myeloid progenitors from healthy Fas lpr/lpr hMRP8bcl-2 mice with (proto-) oncogenes found in human AML will be tested as candidates for leukemogenic collaboration. cDNAs differentially expressed between leukemic and non-leukemic blast cells will be identified through microarray analyses, and candidate genes will be tested as oncogene candidates. Eventually, human AMLs will be screened for homologous gene defects.

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

- **Project Title: MOLECULAR PROFILING IN LEUKEMIA**

  Principal Investigator & Institution: Staudt, Louis; Ohio State University 1960 Kenny Road Columbus, Oh 43210

  Timing: Fiscal Year 2003; Project Start 13-MAY-2003; Project End 31-MAR-2009

  Summary: (provided by applicant): **Acute myeloid leukemia** (AML), acute lymphoblastic leukemia (ALL) and chronic lymphocytic leukemia (CLL) each appear to be heterogeneous at the molecular level (Bloomfield and Caligiuri, 2000). During the past two decades, there has been considerable progress in identifying cytogenetic and molecular markers that can predict outcome following standard treatment for a fraction of patients with AML, ALL, or CLL. However, there still remains a sizable fraction of cases for which molecular predictors of prognosis are not clinically useful, because the malignant clone either lacks such an abnormality or because the abnormality is too infrequent to correlate with clinical outcome. The CALGB is a leader in using cytogenetic and molecular markers to stratify patients based on the risk of failure with standard treatment, and the identification of such indicators has become central to assignment of the appropriate therapy. This trend is likely to become even more critical in the future as more and more targeted therapies that are only active in molecularly defined subsets of patients become available in the clinic. Thus, a very high priority for the CALGB is to develop better and more robust molecular means to predict outcome in the hematologic malignancies. We will do this in conjunction with the Leukemia Committee, as described in that proposal. We hypothesize that genetic expression

profiling using microarrays of diagnostic AML, ALL, and CLL samples that lack cytogenetic or molecular markers predictive of clinical outcome can identify a genetic expression profile or "signature pattern" that can be used to predict clinical outcome following standard therapy. A corollary to this hypothesis is that such a molecular profile could then be used for risk stratification of treatment and ultimately to improve clinical outcome in patients with AML, ALL, and CLL. Also, we hypothesize that Restriction Landmark Genomic Scanning (RLGS) can be used to identify prognostically significant DNA methylation patterns in CLL, with the same implications for clinical outcome.

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- **Project Title: MOLECULAR STUDIES OF SEVERE CONGENITAL NEUTROPENIA**

  Principal Investigator & Institution: Aprikyan, Andrew Ag.; Medicine; University of Washington Grant & Contract Services Seattle, Wa 98105

  Timing: Fiscal Year 2002; Project Start 13-JUL-2001; Project End 30-JUN-2006

  Summary: (provided by applicant) Severe congenital neutropenia (SCN) is characterized by a selective decrease in the number of circulating1 neutrophils associated with recurrent fevers, chronic oropharyngeal inflammation and repeated severe infections. Characteristically these patients have monocytosis, thrombocytosis and mild anemia, unless they have a severe infection. SCN is usually diagnosed in early childhood and may evolve to **acute myeloid leukemia.** The severity of symptoms and risk of serious infections are in general inversely proportional to absolute neutrophil counts. Neutropenia occurs because of impaired formation and reduced delivery of neutrophils from the bone marrow to the peripheral circulation. We have recently described mutations in neutrophil elastase (NE) in 21 of 24 patients with SCN. All patients with family history of SCN and more than 90 percent of sporadic cases carry mutations in neutrophil elastase gene observed that bone marrow myeloid progenitor cells from SCN patients are characterized by a significantly accelerated rate of apoptosis and a transition block from G1 to S phase of the cell cycle. We have also demonstrated that expression of mutant NE in hematopoietic progenitor cells triggers apoptotic cell death. Recently, we identified novel and previously reported point mutations in granulocyte colony-stimulating factor receptor (G-CSFR) in 6 of 7 SCN patients with elastase mutation who evolved to develop **acute myeloid leukemia** (AML). The research goal of this proposal is to understand the molecular mechanism of accelerated cell death and abnormal cell cycle progression in pathogenesis of SCN and its evolution to AML. We will expand our current studies of the cellular mechanism of SCN by examining apoptosis and cell cycle arrest of hematopoietic progenitor cells from a larger number of patients with SCN and SCN/AML with autosomal dominant and autosomal recessive mode of inheritance including patients from the original Kostmanns family. We will further delineate the cellular defect in SCN by focusing on more primitive bone marrow progenitor cell subpopulations and will determine subcellular localization of mutant genes in the bone marrow cells from patients with SCN and SCN/AML. Diversity of NE and G-CSFR mutations in this cohort of patients will also be examined. We will establish myeloid progenitor cell lines with inducible expression of mutant genes, which will enable a comprehensive investigation of the molecular events mediating dysregulatory effects of mutant neutrophil elastase and mutant G-CSFR. These models will be useful for development of novel therapeutic strategies for treatment of severe congenital neutropenia and prevention of its evolution to **acute myeloid leukemia.**

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- **Project Title: MOLECULAR TAXONOMY OF PEDIATRIC AND ADULT ACUTE LEUKEMIA**

  Principal Investigator & Institution: Willman, Cheryl L.; Director, Univ Cancer Research and Treat; Pathology; University of New Mexico Albuquerque Controller's Office Albuquerque, Nm 87131

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

  Summary: Although remarkable advances have been made in the treatment of the acute leukemias, particularly resistant forms of leukemia remain. In 1999, 28,000 children and adults in the U.S. will be diagnosed with leukemia and 21,000 will die of their disease. This variability in clinical response is due in part to the tremendous heterogeneity of the disease itself. Traditionally classified solely on the basis of morphology and cytochemistry, the acute lymphoid or lymphoblastic leukemias (ALL) and the acute myeloid leukemias (AML) are characterized by highly variable clinical and biologic behavior, immunophenotypes, and chromosomal abnormalities. Striking differences in outcome may be seen in cases with the same cytogenetic profile, implying that more subtle genetic abnormalities also impact disease biology and response. We hypothesize that cDNA microarray technology will yield quantitative, orderly, and systematic gene expression profiles that can be used to design more clinically relevant classification schemes and to predict therapeutic response. By conducting correlative science studies accompanying NCI-sponsored clinical trials in children and adults affected by acute leukemia for the Pediatric Oncology Group, Children's Cancer Study Group, and Southwest Oncology Group, and by maintaining the largest leukemia tissue repositories in the world, we are poised to propose the following specific aims: 1. To Further Optimize cDNA Microarray Technology for Studies in Primary Human Leukemia Samples. 2. To Characterize the Molecular Variations Among Highly Selected Acute Leukemia Cases Using at Least 30,000 Genes. Cases have been selected using two approaches: 1) therapeutic response/resistance and 2) the presence of specific cytogenetic abnormalities. Study sets in AML include: 1) patients with "primary resistant" disease; 2) patients in long-term remission; 3) paired pre-treatment and relapse samples; 4) patients responding or failing specific treatment regimens; and 4) cases selected by genotype [t(8.21), inv(16), t(15;17), t(4;11), t(9;11), and complex]. In ALL, cases are being selected prospectively using two approaches: 1) the presence of residual disease vs. complete molecular response during the treatment course using automated quantitative molecular monitoring methods; and 2) by genotype [hyperdiploid, t(12;21), t(9;22), t(1;19), and t(4;11)]. 3. To Apply Multivariate Clustering Methods to Group Acute Leukemias That are Coherent in their Expression Patterns. 4. To Use Automated Quantitative "Real-Time" PCR Technologies to Validate cDNA Microarray Analyses. 5. To Use High Performance Computing and Informatics Technologies to Link Large Genomic Data Sets with Clinical Databases. All leukemia samples have associated clinical databases containing detailed patient information, laboratory data (cytogenetics, correlative scientific studies), and therapeutic response data. Our experienced clinical trials biostatisticians will work with the UNM High Performance Computing Center (a National Supercomputing Facility) and Sandia National Laboratory (both world leaders in massively scalable parallel computing, statistics, informatics, and visualization tools) to meet this aim.

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

- **Project Title: MONOCLONAL ANTIBODY FOR TREATMENT OF LEUKEMIA**

  Principal Investigator & Institution: Ball, Edward D.; Professor and Chief; Cancer Center; University of California San Diego La Jolla, Ca 920930934

Timing: Fiscal Year 2002; Project Start 01-JUN-1983; Project End 30-JUN-2005

Summary: (provided by applicant): Over the past 17 years of this grant, we have produced a large number of monoclonal antibodies (mAb) to myeloid-associated antigens expressed on myeloid leukemia cells. These mAb have been used clinically for the diagnosis and therapy of **acute myeloid leukemia** (AML). One of the mAb, 251, directed to the CD33 antigen specific for myeloid cells, has been incorporated into bispecific antibodies (BsAb) conjugated to either an anti-CD64 or an anti-CD 16 mAb directed to different Fe receptors. These BsAb mediate antibody-dependent cellular cytotoxicity (ADCC) and phagocytosis of myeloid leukemia cells by normal monocytes through Fe receptor- mediated processes. We now propose to focus on the further development of these and an additional BsAb, all targeting CD33 and one of three Fe receptors, for clinical application in the therapy of AML. Here, we will develop an additional BsAb using the same anti-CD33 mAb and an anti-CD89 (Fc alpha receptor) mAb. We will directly compare the relative activities of the three BsAb, all targeting CD33, in vitro for mediating ADCC, phagocytosis, and killing of AML progenitor cells (Specific Aim 1). We will also compare the activities of the three BsAb in a murine/human AML xenograft model (Aim 1). These studies will focus on the relative potency of each BsAb with its unique effector cell population (monocytes, neutrophils, or natural killer cells). In Specific Aim 2 we will focus on the biology of the CD33 antigen and the effects of BsAb on its function. Based on preliminary and published data, CD33 has been determined to be a negative regulator of leukemia cell growth. We will study the mechanisms of action of BsAb. We will examine the molecular effects of BsAb binding to CD33, CD 16, CD64, and CD89 antigens and downstream mediators of cellular function in normal and leukemia cells. In Aim 3, we will extend the observations from Aim 2 to studies on cells from patients entered on a Phase I study of anti-CD33xanti-CD64 BsAb. We will test the hypothesis that the levels of expression of CD33 and CD64 predict the effects of BsAb binding in vivo. At completion of the study, rational planning for clinical trials of BsAb in patients with AML with the most promising BsAb targeting the CD33 antigen will be possible.

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

- **Project Title: MYELOID DEVELOPMENT IN THE ZEBRAFISH**

  Principal Investigator & Institution: Lyons, Susan E.; Internal Medicine; University of Michigan at Ann Arbor 3003 South State, Room 1040 Ann Arbor, Mi 481091274

  Timing: Fiscal Year 2002; Project Start 07-SEP-2002; Project End 30-JUN-2005

  Summary: (provided by applicant): The goal of this work is to study the molecular steps essential for myeloid lineage development in order to better understand both normal hematopoiesis and leukemogenesis. The zebrafish vertebrate model was chosen since its optical clarity allows observation throughout development; genetic manipulations of the embryos can be performed easily; and phenotype-driven, forward genetic analyses are feasible. The long-term objective of this study is the analysis of myeloid development in the zebrafish and the identification and characterization of zebrafish mutants with defects in the myeloid pathway. Defined translocations have been identified in 45 percent of acute leukemias. Many of these translocations involve genes vital to normal hematopoiesis. However, the alterations responsible for the majority of leukemias are still not known. Therefore, we hypothesize that characterization of myelopoiesis and the identification of genes required for determination of the myeloid program will provide insights into the lesions in **acute myeloid leukemia** (AML). The specific aims of the project are as follows: 1. To assess the function of a novel, myeloid-specific zebrafish transcription factor, c/ebp1, and to place it within the myeloid developmental pathway.

Both over-expression and loss of expression approaches will be used to test the hypothesis that c/ebp1 plays an essential role in myeloid development. Currently available myeloid markers will be used for RNA in situ hybridization experiments combined with functional assays. 2. To identify zebrafish mutants with defects in myeloid development in an ENU mutagenesis. The screening will utilize whole-mount RNA in situ hybridization with the general myeloid marker, l-plastin. A zebrafish mutant lacking l-plastin expression has already been identified in our pilot screen and will be characterized and the gene identified through traditional positional cloning techniques.

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- **Project Title: NK CELL RECOGNITION OF LEUKEMIA BLASTS AND IL-2 THERAPY**

  Principal Investigator & Institution: Farag, Sherif S.; Assistant Professor; Internal Medicine; Ohio State University 1960 Kenny Road Columbus, Oh 43210

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

  Summary: (provided by applicant): Approximately 20-25% of patients with **acute myeloid leukemia** (AML) are cured following intensive chemotherapy. Interleukin (IL)-2, administered to AML patients in remission, has been investigated as a means of potentially reducing relapse and improving outcome. IL-2 in vivo expands and activates natural killer (NK) cells, which do not require the recognition of leukemia-specific antigens for killing of leukemic cells. Recent understanding of the importance of NK cell receptors (NKR) for the recognition and lysis of target cells, however, suggests that not all patients are likely to benefit from this immunotherapy strategy. Recognition and lysis of leukemic cells by NK cells is regulated by a balance of activating and inhibitory surface receptors that interact with specific MHC class I and class I-like ligands on target cells. Our preliminary data indeed suggests that primary AML cells, and not only cell lines, express ligands to the activating NKG2D receptor of NK cells. Furthermore, that expression of these ligands by AML is heterogeneous, in keeping with the molecular heterogeneity of the disease. We hypothesize that only leukemic cells that express high levels of activating ligands and/or low levels of inhibitory ligands are susceptible to autologous NK cell lysis, and that patients with such leukemic blasts are those most likely to benefit from IL-2 therapy. To investigate this hypothesis, we propose to perform correlative studies on samples procured from AML patients enrolled on Cancer and Leukemia Group B studies of IL-2 immunotherapy, investigating the relationship between the expression of known important NK cell activating and inhibitory ligands on leukemic blasts, in vitro susceptibility of AML cells to autologous IL-2 expanded NK cells, and clinical outcome. Specifically, we aim to 1) Correlate the in vitro lysis of pre-treatment AML blasts by IL-2 in vivo expanded NK cells with relapse-free survival (RFS) following IL-2 therapy, 2) Correlate the expression of inhibitory (MHC class I) and activating ligands on AML blasts with RFS, and 3) Compare the susceptibility to NK cell lysis of leukemic blasts obtained at diagnosis and at relapse. The results of our studies may provide a means of identifying which subset of AML cases are susceptible to IL-2 therapy, and therefore, may ultimately assist in the better selection of patients for NK cell-based therapies.

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

- **Project Title: NPM/MLF1 IN LEUKEMIA AND NORMAL DEVELOPMENT**

  Principal Investigator & Institution: Morris, Stephan W.; Associate Member; St. Jude Children's Research Hospital Memphis, Tn 381052794

Timing: Fiscal Year 2002; Project Start 15-DEC-1997; Project End 30-NOV-2003

Summary: The t(3;5) in myelodysplastic syndrome (MDS) and **acute myeloid leukemia** (AML) creates a fusion product in which the amino-terminus of nucleophosmin (NPM), a nucleolar shuttle protein, is linked to the novel protein myelodysplasia/myeloid leukemia factor 1 (MLF1). The NPM portion of NPM-MLF1 contains an oligomerization motif that mediates self- association, association with normal NPM, and nuclear targeting; the importance of these (and other) NPM functions in NPM-MLF1-mediated MDS and AML is unknown. The normally cytoplasmic MLF1 protein, which lacks recognized functional motifs, is expressed in some leukemic cell lines but not in t(3;5)-positive cells; the role of MLF1 in normal hematopoiesis has not been determined. NPM-MLF1 can inhibit the G-CSF- mediated survival and, hence, the differentiation of myeloid precursor cells in a manner consistent with the proposed pathogenesis of MDS; MDS progression to AML probably requires additional mutations that cooperate with NPM-MLF1. To understand how NPM-MLF1 contributes to the genesis of MDS and AML, the funtionally -critical motifs in the NPM and MLF1 portions of the fusion that mediate its ability to block myeloid cell survival/differentiation will first be identified. Next, the hypothesis that NPM-MLF1 interferes with hematopoietic development to produce MDS and AML will be tested in mice programmed to express the fusion; as a corollary, the necessity for cooperating mutations in the induction AML by NPM-MLF1 will be determined and, if required, the involved genes will be identified. Finally, the role of MLF1 in normal growth and development will be defined to better understand how its alteration produces MDS and AML by determining the Mlf1 expression pattern in fetal and adult mice, by targeted disruption of the gene, and by assessing the effects of Mlf1 absence, or its aberrant expression, on hematopoietic differentiation of ES cells in vitro. These studies should yield valuable insight into the regulatory pathways disrupted by NPM-MLF1 in myelodysplastic (preleukemic) cells, and perhaps into the pathobiology of AML in general.

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- **Project Title: NUP98-HOXA9 AND AML**

  Principal Investigator & Institution: Van Deursen, Jan M.; Associate Professor; Mayo Clinic Coll of Medicine, Rochester 200 1St St Sw Rochester, Mn 55905

  Timing: Fiscal Year 2002; Project Start 01-APR-1998; Project End 31-JAN-2003

  Summary: (adapted from the investigator's abstract) The t(7;11) in patients with **acute myeloid leukemia** (AML) generates a fusion gene encoding the amino-terminal NUP98, an FG repeat-containing nuclear pore complex protein (NPC), and the carboxy-terminus of HOXA9, a homeotic transcription factor. The NUP98 portion of NUP98-HOXA9 contains 37 of the 38 FG repeat motif of NUP98. The HOXA9 part contains the HOXA9 DNA-binding domain and a TRP-containing motif that mediates interactions between HOXA9 and other transcription factors. The long term objective is to understand the exact mechanism by which NUP98-HOXA9 contributes to leukemia. To achieve this goal, the functionally critical motifs in the NUP98 and HOXA9 portions of NUP98-HOXA9 that mediate its ability to transform NIH3T3 cell will be defined, as will the proteins that interact with these motifs. The ability of each NUP98-HOXA9 isoform to induce AML in vivo will be tested by genetically engineering mice to express the chimeric proteins. Further, these mice will be bred onto a BXH2 genetic background to identify mutations that cooperate with NUP98-HOXA9 to induce AML. Finally, the normal in vivo functions of NUP98 and HOXA9 will be studied by examining phenotypic effects of loss- or gain-of-function mutations in mice. These studies should

further our understanding of the molecular mechanism of oncogenesis in an expanding subgroup o AML patients with translocations that link nucleoporins to nuclear proteins.

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- **Project Title: ONCOGENES INVOLVED IN ACUTE MYELOID LEUKEMIA DEVELOPMENT**

  Principal Investigator & Institution: Reuther, Gary W.; Comprehensive Cancer Center; University of North Carolina Chapel Hill Aob 104 Airport Drive Cb#1350 Chapel Hill, Nc 27599

  Timing: Fiscal Year 2003; Project Start 03-SEP-2003; Project End 31-AUG-2008

  Summary: (provided by applicant): The goal of this proposal is to identify and characterize novel oncogenes expressed in patients with **acute myeloid leukemia** (AML). The design of this proposal is to position the candidate for an independent career in basic cancer research, with a focus on leukemia, in an academic environment. Working in Dr. Channing Der's laboratory at the University of North Carolina at Chapel Hill has provided an excellent foundation for this career. With a little more guidance from Dr. Der, the candidate will utilize the outstanding resources that Dr. Der's laboratory and the University of North Carolina at Chapel Hill provide, in order to solidify the scientific basis for an independent career in research. The first two specific aims of this research proposal focus on characterizing a novel activator of Ras, RasGRP4, identified by the candidate in a screen for novel oncogenes in AML. RasGRP4 is primarily expressed in myeloid cells suggesting it has a specific role in these cells. Targeted disruption of the gene for RasGRP4 in mice will be utilized to characterize the normal function of RasGRP4. The development of the hematopoietic system of these mice will be analyzed along with signal transduction pathways that may utilize RasGRP4. These studies represent an excellent opportunity to expand the candidate's technical repertoire (e.g., animal model development and analyses of primary hematopoietic cells), by combining the resources provided by the UNC Chapel Hill animal model facility and Dr. Der's expertise on Ras signal transduction. The last aim of this proposal, which will be initiated in the independent phase of the award, is to perform additional screens for oncogenes in AML. AML formation requires two classes of mutations: one that induces cell proliferation and survival, and one that inhibits differentiation. AML1-Eto and CBFb-MYH11, two common oncogenes in AML, are not sufficient to induce leukemia. This proposal describes experiments to identify required mutations, expressed in AML patients whose leukemic cells harbor these fusion proteins, that cooperate with these oncogenes and also to identify members of both classes of AML oncogenes. This will provide an opportunity to expand and improve strategies aimed at identifying novel oncogenes in AML. In summary, this proposal provides an excellent opportunity for the candidate to complete his training to become an independent researcher.

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

- **Project Title: PHARMACOGENETIC STUDIES OF ACUTE MYELOID LEUKEMIA**

  Principal Investigator & Institution: Moysich, Kirsten B.; Assistant Professor; Roswell Park Cancer Institute Corp Buffalo, Ny 14263

  Timing: Fiscal Year 2004; Project Start 21-APR-2004; Project End 31-MAR-2006

  Summary: (provided by applicant): Many academic institutions and Cooperative Groups maintain extensive archives of tumor tissue from patients with matching treatment and clinical outcome information. Such archives have been utilized for

molecular characterizations of specific tumors, as well as prognostic studies aimed at investigating the effect of acquired genetic alterations on clinical outcome measures. There is increasing interest in utilizing these tumor archives in pharmacogenetic studies, which are concerned with assessing the associations between constitutional genetic polymorphisms and treatment-related toxicity and prognosis. Little effort has focused on the appropriateness of using diseased tissue as a source of genomic DNA in pharmacogenetic studies. We believe that an important first step in pharmacogenetic studies that utilize stored tumor tissue as a source of genomic DNA should be to demonstrate concordance between polymorphism measured in diseased and paired non-diseased tissue. Since our long-term interest lies in conducting a pharmacogenetic investigation of **acute myeloid leukemia,** we propose in our primary specific aim to systematically investigate the utility of using archived bone marrow samples for an investigation on the prognostic significance of a panel of genes involved in the pharmacodynamics of AML chemotherapy in a well-characterized group of AML patients. In our secondary specific aim, we propose to utilize the data generated from this methodological investigation for a pilot study on the role of this panel of polymorphisms relevant to AML treatment in toxicity and clinical outcome measures among AML patients. Specifically, we will compare genetic polymorphism data between paired bone marrow and buccal cells from 100 AML patients from Roswell Park Cancer Institute. In the pilot study component of this research we will assess role of genetic polymorphisms encoding for proteins involved in metabolism of chemotherapeutic agents used in the treatment of AML, protection from oxidative damage generated by chemotherapeutic agents, and drug resistance in clinical outcome measures among AML patients. Data generated from this research will guide the design of large-scale pharmacogenetic studies of AML by a) providing data on the appropriateness of using existing bone marrow tissue banks, and b) direct sample size considerations by providing data on potential misclassification of genotype data in bone marrow tissue, as well as preliminary data on the effect of genetic polymorphisms on clinical outcomes.

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- **Project Title: PLZF ONCOPROTEIN COMPLEXES SPECIFIC INTERACTION BLOCKER**

  Principal Investigator & Institution: Watt, Paul M.; Tvw Telethon Institute-Child Health Res for Child Health Research Subiaco,

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

  Summary: (provided by applicant): Several crucial oncoprotein interactions occur largely in tumour cells and thus provide ideal targets for intervention. The proposed project is to develop a model system for a target-specific therapy of leukaemia. The ability to isolate specific blockers of particular protein/protein interactions also provides an opportunity to uncouple complex genetic pathways in mammalian systems, which are relatively intractable to genetic analysis. The dissection of pathways using specific blockers may ultimately provide a useful avenue for identifying and characterizing new drug targets. We have chosen to target one of the known interactions of the oncoprotein, PLZF in the search for specific inhibitors. Complexes containing PLZF are involved in the development of Acute Promyelocytic Leukemia (APL) and **Acute Myeloid Leukemia** (AML). A genetic selection will be used to identify naturally derived peptide sequences which are capable of blocking PLZF/ETO interactions and which do not interfere with other interactions involving the PLZF protein. This technique termed 'dual-bait/reporter reverse two hybrid screening' allows one to select for or against

specific blockers of known interactions in yeast cells. The affinity and specificity of the interaction blockers derived from the screen will be determined using the novel yeast genetic system and by ex vivo assays of functional effects of candidate peptides on repression and growth inhibitory activity of PLZF. Finally, isolation of specific blockers of PLZF interactions may provide leads or the development of new therapeutic agents for the treatment of APL and AML.

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- **Project Title: PPAR-GAMMA NUCLEAR TRANSCRIPTION FACTOR: A NOVEL TARGET FOR LEUKEMIA THERAPY**

  Principal Investigator & Institution: Andreeff, Michael W.; Stringer Professor for Cancer Treatment; University of Texas Md Anderson Can Ctr Cancer Center Houston, Tx 77030

  Timing: Fiscal Year 2003; Project Start 05-AUG-2003; Project End 30-APR-2008

  Summary: New approaches are needed to improve cure rates in adult hematological malignancies. PPARgamma (Peroxisome Proliferator-Activated Receptor Gamma) is a member of the nuclear transcription factor family involved in signaling of differentiation. We have demonstrated that PPARgamma is expressed in the majority of primary human leukemias but not in normal hematopoietic progenitors, and that ligation of PPARgamma induces differentiation, growth arrest and apoptosis in leukemias. We propose to extend our initial studies on the mechanisms and efficacy of PPARgamma signaling in **acute myeloid leukemia** to acute and chronic (CLL) leukemia, with the goal of developing PPARgamma as a novel target for the treatment of hematological malignancies. We are encouraged to pursue this goal by the seminal impact on leukemia therapy that was affected by targeting RARalpha in acute promyelocytic leukemia (APL) with ATRA. First, we will investigate the expression of PPARgamma, in acute and chronic myeloid and lymphoid human leukemias and leukemic stem cells and study the effects of PPARgamma ligands on apoptosis and differentiation. We will determine the effects of combined targeting of PPARgamma and RXR in leukemias, as PPARgamma, and RXR heterodimerization is required to maximize transcriptional activation. In the second aim, we will further elucidate the specific mechanisms of apoptotic cell death and growth arrest that are triggered by PPARgamma, ligation. Preliminary data demonstrate that PPARgamma ligands induce loss of mitochondrial membrane potential and activation of effector caspases. Finally, we propose to initiate Phase I studies using PPARgamma ligands, in combination with rexinoids. These studies will utilize FDA approved PPARgamma and RXR ligands and the new potent triterpenoid CDDO, a novel PPARgamma, ligand that is presently being developed by us with assistance from CTEP/RAID at the National Cancer Institute. The long-term goal of the proposed studies is to determine the molecular, biological and clinical effects of PPARgamma/RXR ligation in human leukemia and to develop the PPARgamma/RXR nuclear receptor system as a novel target for leukemia therapy.

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

- **Project Title: PROTEOMICS SOFTWARE PACKAGE FOR THE DETECTION OF CANCER**

  Principal Investigator & Institution: Sasinowski, Maciek; Incogen, Inc. 263 Mclaws Cir, Ste 200 Williamsburg, Va 23185

  Timing: Fiscal Year 2003; Project Start 01-APR-2003; Project End 30-SEP-2003

  Summary: (provided by applicant): This SBIR project proposes the development of a software package containing bio-computational tools to facilitate accurate diagnosis of

cancer based on classification of proteomics data obtained through mass spectrometry (MS). The software will accept MS data produced from a wide range of instruments but is specifically targeted toward MALDI/SELDI TOF analysis (Applied Biosystems, Ciphergen). The Phase I work will focus on exploring the applicability of various existing and modified statistical approaches for signal conditioning (Wiener filters) and classification (linear discriminant analysis, principal components analysis, support vector machines, Bayes method) of SELDI data derived from analysis of sera from individuals with pediatric Hodgkin's disease and **acute myeloid leukemia.** A software package to perform this task does not currently exist; therefore, the proposed research has significant potential for technical innovation. Cross-validation will be used to obtain an unbiased estimate of the performances of the classifiers. The TRIFT II equipment at the ARC (W&M) will be used to provide high-resolution MS TOF SIMS data to calibrate the SELDI equipment at EVMS. The Phase II project will leverage the research and proof-of-concept tools developed in Phase I to produce a commercial software package that will be licensed to researchers, as well as equipment manufacturers for inclusion with their instruments.

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- **Project Title: REGULATION OF THE HUMAN MDR1 GENE**

  Principal Investigator & Institution: Sikic, Branimir I.; Professor; Medicine; Stanford University Stanford, Ca 94305

  Timing: Fiscal Year 2002; Project Start 08-MAY-2002; Project End 30-APR-2006

  Summary: (PROVIDED BY APPLICANT): MDR1 gene expression is an important prognostic marker in many human cancers. This application focuses on the underlying mechanisms responsible for regulating the expression of MDR1, particularly involving the NF-IL6 family of transcriptional regulators. Aim 1. To Study the Role of NF-IL6 in Activating or Suppressing MDR1 Expression. The hypothesis is that altered expression of NF-IL6 family members in human cancer cells may be responsible for MDR1 activation in these cells. Experimental approaches will include co-transfection of MDR1 promoter constructs and different forms of NF-IL6, quantitative analysis of NF-IL6 family members in nuclear and cytoplasmic extracts, and studies of the phosphorylation status of NF-IL6 species in cellular models. Aim 2. To Study Protein-Protein Interactions Mediated by NF-IL6 in MDR1. An NF-IL6-2 interacting site was mapped in MCF-7 cells within -128 to -75 of the MDR1 P1 promoter, a region which lacks NF-IL6 binding motifs. NF-IL6 may activate the MDR1 promoter through multiple interaction sites. Physical interactions among NF-IL6 family members, the Y-box-associated factors (NF-Y and YB-1), and AP1 (c-fos and c-jun) will be verified in vitro by GST pull down experiments utilizing a GST-NF-IL6 fusion protein to precipitate factors in nuclear extracts of MDR cell lines. Once protein interactions are established, their functional role in regulating the chromosomal MDR1 gene will be examined in stable transfectants containing MDR1 constructs. Aim 3. To Investigate a Novel Activator Involved in MDR1 Regulation. The hypothesis is that that there is a novel binding protein, other than NF-IL6, responsible for maintaining basal promoter activity in MCF-7 cells. The plan is to identify the protein and its gene binding to the -148 to -140 element by mobility shift assays as well as the yeast one-hybrid system. Sense and antisense cDNAs for this binding protein will be transfected into both MCF-7 and MCF-7/ADR cells to test their capacity to activate or modulate MDR1 expression. Aim 4. To Study MDR1 Regulation in Clinical Specimens. The focus will be on **acute myeloid leukemia** (AML) as a clinical model for MDR1 expression. MDR1 will be analyzed by rtPCR and flow cytometry. NF-

IL6 members will be quantitatively analyzed in both nudear and cytoplasmic extracts of AML.

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- **Project Title: RIBONUCLEOTIDE REDUCTASE ANTISENSE STRATEGY IN AML**

  Principal Investigator & Institution: Marcucci, Guido; Assistant Professor; Internal Medicine; Ohio State University 1960 Kenny Road Columbus, Oh 43210

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

  Summary: (provided by applicant): Most patients with **acute myeloid leukemia** (AML) relapse and ultimately die as a consequence of refractory or resistant disease. Salvage chemotherapy at conventional doses may induce a short-term remission, but this approach is generally not curative. For those patients who are not candidates for allogeneic BMT the prognosis remains dismal and new therapeutic strategies targeting specific leukemogenic mechanisms are highly needed to improve the current clinical results. In the past few years, we have successfully applied the antisense strategy to down-regulate expression of distinct target genes that contribute to chemoresistance in myeloid blasts. Here we propose to explore the activity of a novel ribonucleotide reductase (RR) antisense, GTI-2040, in combination with high-dose ARA-C (cytarabine arabinoside) in refractory or relapsed AML. RR is an enzyme operative in the synthetic pathway of deoxyribonucleotides and a potential key factor in induction of chemoresistance to ARA-C, a nucleoside analog incorporated in a variety of AML chemotherapy regimens. We seek to understand the relation between plasma and intracellular concentration of GTI-2040 and how this correlates to RR down-regulation, patient toxicity and disease response. Specific Aim #1 will conduct a phase I study of GTI-2040 in combination with high-dose ARA-C in refractory or relapsed AML. The ultimate goal is to assess the feasibility of this combination and recommend a dose for future phase II studies in this patient population. Specific Aim #2 will evaluate the plasma pharmacokinetics of GTI-2040 using a sensitive ELISA-based assay that we have developed at OSU. This assay will also allow us to measure intracellular concentrations of GTI-2040 in selected leukemia cells from patients enrolled on this protocol. Specific Aim #3 will examine the correlation between plasma and intracellular concentrations of GTI-2040 with toxicity, disease response and biological endpoints such as down-regulation of the antisense target (i.e., the R2 subunit of RR) at the mRNA and protein levels, changes in RR enzymatic activity and levels of apoptosis in selected leukemia cells collected from patients enrolled in this protocol. It is expected that the analysis of these data will allow us to elucidate the intrinsic mechanisms of the antitumor activity of the antisense compounds and plan their incorporation in future therapeutic strategies for AML patients.

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

- **Project Title: ROLE OF AML1/ETO IN HEMATOPOIESIS AND LEUKEMOGENESIS**

  Principal Investigator & Institution: Mulloy, James C.; Sloan-Kettering Institute for Cancer Res New York, Ny 100216007

  Timing: Fiscal Year 2002; Project Start 16-MAY-2001; Project End 31-JAN-2003

  Summary: The AML 1/ETO fusion protein is causally implicated in the pathogenesis of 40% of acute myeloid leukemias of the M2 subtype, and accounts for 12% of human AMLs overall. The fusion gene is compromised of the amino-terminal portion of the AML1 (CBFA2) gene on chromosome 21 and the nearly full coding region of ETO gene

on chromosome 8. Aml1/Eto interferes with the function of the transcription factor, CBF, in a dominant negative fashion, presumably by its ability to bind to the heterodimeric transcription partner CBF beta and repress transcription through CBF enhancer elements. Mice deficient in AML1 or CBF BETA lack definitive hematopoiesis, and these mice die during embryogenesis. Similarly, mice engineered to express a leukemic fusion protein that interferes with CBF function die from a similar phenotype, complicating the development of an animal model of AML. Recent advances in retroviral gene delivery systems, hematopoietic stem cell biology, and immunodeficient animal development have made it possible to overexpress genes of interest in human and murine stem cells and use these cells to reconstitute the immune system of recipient animals. The ultimate objective of this work is the development of murine model AML, specifically of AML associated with expression of AML1/ETO (Specific Aim 1). A murine retovirus optimized for expression in stem cells will be used, and the green fluorescent protein will be co-expressed from the same mRNA using an IRES element, to facilitate identification of transduced cells. Both human and murine stem cells will be used in these studies, and the appropriate animal model will be chosen to allow the growth of transformed cells in vivo. In vitro studies will also be performed to determine the effects of AML1/ETO over-expression on normal hematopoiesis (Specific Aim 2). Using specific combinations of cytokines and stromal layers, the investigator will determine which hematopoietic lineage is affected by AML1/ETO expression. Mutants of AML1/ETO will also be included in the system, to decipher which signaling pathways are important in AML1/ETO-induced leukemia in vivo. mRNA from human stem cells expressing AML1/ETO will be used for differential hybridization screening of high-density microarrays to identify target genes regulated by AML1/ETO (Specific Aim 3). These target genes will be evaluated for their contribution for the phenotype elicited by expression of AML1/ETO in human stem cells, using the assays mentioned above. Taken together, these data will provide detailed information on the functional role of AML1/ETO in both hematopoeisis and leukemogenesis. The establishment of a small animal model of AML will greatly enhance our ability to develop and test treatment strategies and drugs that may be useful in the therapy of AML.

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- **Project Title: ROLE OF MN1 TEL AND TEL IN LEUKEMOGENESIS**

  Principal Investigator & Institution: Grosveld, Gerard C.; Chair; St. Jude Children's Research Hospital Memphis, Tn 381052794

  Timing: Fiscal Year 2002; Project Start 01-JUL-1997; Project End 30-JUN-2006

  Summary: (provided by applicant) TEL (ETV6) is a frequent target of chromosomal translocations in hematopoietic malignancies and some solid tumors. The recurrent t(1 2;22), which is associated with myeloproliferative disorders and **acute myeloid leukemia,** results in the creation of the MN 1-TEL fusion gene in which the sequence encoding the N-terminal region of the transcription factor TEL is replaced by almost the entire coding sequence of the transcriptional coactivator MN1. MN1-TEL can transform fibroblasts, and recent findings suggest that this fusion protein increases the proliferation rate of primitive hematopoietic progenitors in vitro. However, transplantation of mouse bone marrow cells transduced with an MN1-TEL--containing retrovirus into lethally irradiated recipients does not result in overt hematologic abnormalities or leukemia. This result suggests that secondary genetic lesions must cooperate with MN1-TEL to transform primitive hematopoietic progenitors. Therefore, retroviral rnutagenesis of MN1-TEL--expressing boneS marrow cells will be performed to identify those genetic lesions that cooperate with MN 1-TEL in the induction of

leukemia (Specific Aim 1). Earlier work has identified a novel TEL homolog, TEL2, which is primarily expressed in human fetal liver and bone marrow cells. TEL2 has extensive sequence homology with TEL; although both proteins form oligomers via their pointed domains and repress transcription through the same DNA recognition sequence, they have distinct biological activities. Notably, overexpression of TEL2 stimulates the proliferation of murine hematopoietic progenitors in vitro. Because genetic evidence suggests that TEL acts as tumor suppressor, experiments will test the hypothesis that the loss of TEL results in an altered ratio of TEL:TEL2 to TEL2:TEL2 oligomers and that this alteration directly results in increased proliferation of affected cells (Specific Aim 2). Together the results of the proposed studies should provide insight into the pathways involved in MN1-TEL-associated leukemia and TEL's mechanism of tumor suppression. The murine models generated in these studies should be valuable tools in the development of new therapies for t(1 2;22)-associated myeloid diseases.

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- **Project Title: ROLE OF THE PNH PHENOTYPE IN LEUKEMIC TRANSFORMATION**

  Principal Investigator & Institution: Bessler, Monica; Barnes-Jewish Hospital Ms 90-94-212 St. Louis, Mo 63110

  Timing: Fiscal Year 2002; Project Start 20-JAN-2001; Project End 31-DEC-2005

  Summary: (adapted from the applicant's abstract): Paroxysmal nocturnal hemoglobinuria (PNH) is a blood disorder, which is caused by the clonal expansion of a hematopoietic progenitor cell that carries a somatic mutation in the X-linked PIGA gene. It presented classically with hemoglobinuria due to intravascular hemolysis, thrombotic complications, and pancytopenia. The PIGA gene encodes a protein subunit of a glycosyltransferase essential in the synthesis of glycosyl phosphatidylinositol (GPI) anchor molecules. Patients with PNH therefore have a proportion of blood cells deficient in all GPI-linked surface molecules. PNH is frequently found in patients with aplastic anemia (AA) and in patients with myelodysplasia (MDS). Although not a neoplastic disease on its own, patients with PNH have an increased risk of developing **acute myeloid leukemia** (AML). Promoted by the clinical association of PNH with AA, MDS, and AML, we raised the hypothesis that a PIGA gene mutation alone does not cause clonal expansion or leukemic transformation. But due to their inability to like certain proteins to the cell surface through a GPI-anchor PNH cells escape immuno surveillance and cell death that causes bone marrow aplasia in AA and controls neoplastic cell growth in early leukemogenesis. In the proposed research we will use a mouse model that closely mimics the human disease and investigate the association of PNH with MDS and AML. We will obtain mice with blood cells lacking GPI-linked proteins by disrupting the murine Piga gene in early hematopoietic progenitor cells in the bone marrow using the Cre-loxP system. By this approach we will generate two types of mice, one with all blood cells deficient in GPI-linked proteins whereas the other will have both PIGA (+) and PIGA(-) circulating blood cells. We will then compare PIGA(+) and PIGA(-) hematopoiesis in these mice in vitro and in vivo under a variety of circumstances, including the administration of stimuli that trigger cell death along with agents known to cause leukemia transformation. Competition between cells expressing wild type Piga and those expressing the recombined Piga allele will enable us to uncover even subtle differences in cell death and proliferation in any stages of hematopoietic differentiation. These experiments will demonstrate whether PIGA(-) blood cells are more resistant to specific stimuli that activate apoptotic cell death and

whether mice with PIGA(-) blood cells develop leukemia earlier and more frequent compared to mice with phenotypically normal blood cells. In this way we hope to identify the factors that differentially influence growth and death of PNH and normal hematopoietic progenitor cells and to elucidate mechanisms that may lead to leukemia transformation in patients with PNH. The availability of a mouse model for PNH will provide us with a powerful tool to test new therapeutic agents for the treatment of PNH, PNH/MDS, PNH,AML and possibly other clonal blood disorders.

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

- **Project Title: RUNX1 GENE DOSAGE AND COOPERATIVITY IN LEUKEMIA**

  Principal Investigator & Institution: Gilliland, D Gary.; Associate Professor; Brigham and Women's Hospital 75 Francis Street Boston, Ma 02115

  Timing: Fiscal Year 2002; Project Start 15-JUN-2002; Project End 31-MAR-2007

  Summary: (provided by applicant): The central hypothesis of this proposal is that mutations and gene rearrangements that affect gene dosage of the hematopoietic transcription factor RUNXI cooperate with activating mutations in FLT3, KIT and RAS to cause **acute myeloid leukemia.** During the previous funding period for this proposal, we used a positional cloning strategy to demonstrate that mutations in the hematopoietic transcription factor R UNXI are responsible for the familial platelet disorder with propensity to develop **acute myeloid leukemia** (FPDIAML syndrome, MIM 601399). Subsequently, we and others have demonstrated similar loss of function mutations in RUNXI in sporadic cases of **acute myeloid leukemia.** Analysis of several FPD/AML pedigrees supports haploinsufficiency of R UNXI as the cause of the FPD/AML syndrome. However, in sporadic cases of leukemia, both alleles of R UNXI may be mutated, indicating that complete loss of function of RUNXI may contribute to progression to AML. In addition, several pedigrees and sporadic cases of AML harbor RUNXI mutations that may be partially functional or have transdominant effects. Against this backdrop, it has recently been appreciated that increased dosage of RUNX] may also contribute to pathogenesis of hematopoietic neoplasia. In this proposal, we will explore the role of RUNX] dosage effects in the pathogenesis of human leukemia. We anticipated that this analysis would be difficult, in part because of abundant evidence that, although mutations and gene rearrangements of RUNX1 are frequent in leukemia, none of these are sufficient to cause AML. We reasoned that mutations affecting RUNX I dosage may impair hematopoietic differentation, but that additional mutations would be required to confer proliferative and/or survival advantage to these cells. We have demonstrated the presence of activating mutations in the FLT3 and c-KIT receptor tyrosine kinases, and in K-RAS, in human leukemias associated with RUNX1 point mutations. Based on these observations we will pursue the following Specific Aims: 1.Characterize the leukemogenicity of loss or gain of function of Runxl in the mouse; 2. Characterize leukemic potential of activating mutations in hematopoietic receptor tyrosine kinases and K-RAS using murine models; and 3. Characterize cooperativity between activating mutations in FLT3, KIT and K-RAS with mutations affecting Runxl gene dosage in murine models of leukemogenesis.

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

- **Project Title: RUNX1 IN MYELOID DEVELOPMENT**

  Principal Investigator & Institution: Zhang, Dong-Er; Associate Professor; Beth Israel Deaconess Medical Center St 1005 Boston, Ma 02215

  Timing: Fiscal Year 2003; Project Start 16-MAY-2003; Project End 30-APR-2008

Summary: The overall goal of this proposal is to understand the role of AML1 in myeloid development. AML1 expression initiates from the commitment of hematopoietic stem cells and continues during the maturation of myeloid cells. It regulates the promoter activity of several important myeloid specific genes, such as IL-3, GM-CSF, and M-CSF receptor. The analysis of AML1 deficient mice demonstrates that AML1 plays the most fundamental role for definitive hematopoiesis. AML1 gene is originally cloned from human **acute myeloid leukemia** cells. Further analysis indicate that AML1 is the most common transcription factor involved in various forms of chromosomal translocations associated with either **acute myeloid leukemia** or acute lymphoid leukemia. We have demonstrated the synergistic effect of AML1 with C/EBP and PU.1 on the activation of myeloid specific gene expression, localized the critical domains of AML1 for the synergy, analyzed the differential gene expression in AML1 fusion gene knock-in mice and in a myeloid cell line. Furthermore, we have demonstrated using transgenic mouse models that AML1 fusion protein directly contributes to the development of **acute myeloid leukemia** but itself is not sufficient to cause leukemia. In this funding period, we propose to study the role of AML1 in myeloid development by analyzing the regulation of its function by phosphorylation and critical additional mutations associated with AML1 fusion protein in myeloid leukemia development. The results of these studies will significantly improve our understanding of the molecular mechanisms by which the myeloid lineage undergoes commitment and differentiation. The specific aims of this proposal are 1) define the function of AML1 phosphorylation, 2) study the mechanism of AML1 - C/EBP synergy during myeloid leukemogenesis, 3) identify additional mutations and signaling pathways cooperated with the AML1 fusion protein in myeloid leukemia.

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- **Project Title: STAT ACTIVATION IN LEUKEMIAS**

  Principal Investigator & Institution: Zuckerman, Kenneth S.; Professor; Internal Medicine; University of South Florida 4202 E Fowler Ave Tampa, Fl 33620

  Timing: Fiscal Year 2002; Project Start 01-FEB-2001; Project End 31-JAN-2006

  Summary: (Applicant's Abstract) The first purpose of this project is to understand the molecular mechanisms responsible for the constitutive activation of the Janus kinase (JAK)/signal transducers and activators of transcription (STAT) signal transduction pathways in some cases of **acute myeloid leukemia** (AML), acute lymphoblastic leukemia (ALL), and chronic myelogenous leukemia (CML). The second purpose of this project is to determine the importance of constitutive JAK2/STAT5 activation in development and maintenance of the leukemic phenotype, both in vitro and in vivo. The primary hypotheses being tested are that specific activating mutations that lead to constitutive activation of JAK/STAT signal transduction pathways are responsible for the development and/or maintenance of leukemic cell survival and proliferation, and that, in leukemic cells expressing constitutively activated STAT5, inhibition of STAT5 activation or function. Three specific aims are proposed to test these hypotheses. Specific Aim 1 is to determine the mechanism(s) of constitutive activation in the HEL/Dami and Meg-01 human leukemic cell lines. Specific Aim 2 is to determine whether constitutive JAK/STAT signaling pathway activation plays an important role in maintenance of the leukemic phenotype of primary human AML cells. Specific Aim 3 is to determine the ability of double-stranded "decoy" oligonucleotides containing the STAT5 binding domain to inhibit the unregulated survival and proliferation of leukemic cells in vivo. The models to be tested include: (1) human HEL/Dami and Meg-01 cell lines implanted in sublethally irradiated NOD/SCID mice; (2) tet-off bcr/abl transgenic mice, which

develop leukemia when mice are deprived of tetracycline in their drinking water (obtained from Dan Tenen); and (3) mice transplanted with bone marrow cells transfected with TEL/JAK2 or TEL/ABL retroviruses, which result in development of leukemias that have constitutively activated STAT5. These studies should lead to new understanding approaches for treatment of leukemias in which STAT activation plays a role in maintenance of the leukemic phenotype.

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- **Project Title: STRUCTURAL BIOLOGY OF AML1 (CBFA2) AND AML1-ETO**

  Principal Investigator & Institution: Bushweller, John H.; Associate Professor; Mol Physiol/Biological Physics; University of Virginia Charlottesville Box 400195 Charlottesville, Va 22904

  Timing: Fiscal Year 2004; Project Start 04-MAR-2004; Project End 28-FEB-2009

  Summary: (provided by applicant): Core binding factors (CBFs) are heterodimeric transcription factors consisting of DNA-binding RUNX (AML1) subunits and a non-DNA-binding CBFB subunit. All four genes that encode RUNX subunits (RUNX1, RUNX2, RUNX3) and the gene encoding the CBFB subunit are essential for normal development, and are mutated in human disease. RUNX1 and CBFB are required for hematopoiesis, and are mutated in 25%-30% of human leukemias. RUNX1 and CBFB are proto-oncogenes commonly activated in human leukemias. The reversion and translocations identified in these genes are associated with ~30% of de novo acute myeloid leukemias (AML) in humans. The t(8;21) associated with 12-15% of AML cases generates a novel fusion protein, AML1-ETO, containing the N-terminal 177 amino acids of RUNX1 including the Runt domain and virtually all (577 amino acids) of ETO. Heterozygous knock-in of AML1-ETO was lethal indicating that it is a dominant negative. An inducible mouse model of AML1-ETO shows that it highly predisposes mice to the development of leukemia. We are proposing to test the role of 2 functional domains of AML1-ETO. Aim 1: Structural characterization of functional domains of AML1-ETO (HHR and MYND domains) to test the hypothesis that each domain is essential for the dominant negative phenotype of AML1-ETO. Aim 1 proposes to solve the structures of these two domains (HHR and MYND) by themselves or as functional complexes using NMR spectroscopy or x-ray crystallography. Aim 2: Biochemical characterization of functional domains of AML1-ETO (HHR and MYND domains) to test the hypothesis that each domain is essential for the dominant negative phenotype of AML1-ETO. Aim 2 proposes to measure the binding constants of these individual domains and longer forms with interacting proteins and with DNA using isothermal titration calorimetry and surface plasmon resonance methods, including identification of hot spots for interaction by Ala point mutagenesis. Aim 3: In vivo characterization of functional domains of AML1-ETO (HHR and MYND domains) to test the hypothesis that each domain is essential for the dominant negative phenotype of AML1-ETO. Based on the identification of highly specific point mutations that disrupt particular interactions of AML1-ETO, we can surgically test the role of each of these functions in vivo.

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

- **Project Title: STRUCTURE-FUNCTION OF PROTEIN DEACETYLASES**

  Principal Investigator & Institution: Marmorstein, Ronen; Professor; Wistar Institute Philadelphia, Pa 191044268

  Timing: Fiscal Year 2004; Project Start 01-MAR-2004; Project End 28-FEB-2009

Summary: (provided by applicant): Histone deacetylases (HDACs) were first identified through their ability to deacetylate the epsilon amino group of specific lysine residues within the N-terminal tail regions of histones to promote transcriptional repression or gene silencing. Several deacetylase enzymes that have sequence homology to HDACs have more recently been shown to deacetylate non-histone protein targets in vivo such as the p53 tumor suppressor protein for DNA repair regulation and alpha-tubulin for maintenance of cell integrity, suggesting that these proteins have even broader function than transcriptional regulation. The HDAC proteins fall into three classes and employ two different catalytic mechanisms. Class I and II HDACs show considerable sequence homology within the catalytic domain and do not use a cofactor for catalysis. The class III HDACs belong to the Sir2 protein family and show primary sequence and structural divergence with the class I/II HDACs. In addition, the Sir2 proteins employ a novel catalytic mechanism, whereby protein deacetylation is accompanied by NAD+ hydrolysis generating a novel O-acetyl-ADP-ribose intermediate and nicotinamide. A particularly exciting area of HDAC research relates to their implicated role in human cancer, including the involvement of the human class I HDACs in **acute myeloid leukemia** and the class III HDACs in the regulation of the p53 tumor suppressor protein. Indeed, HDAC inhibitors are currently in clinical trails as anticancer agents and hydroxamic acid-based HDAC inhibitors, such as SAHA and TSA, have already shown promising activity against several different solid tumors at well-tolerated doses. Despite the important biological role of HDAC proteins and their involvement in human cancer, their mechanism for catalysis, mode of substrate-specific binding, and the biochemical consequence of HDAC deacetylation is poorly understood. This lack of mechanistic information stems from a paucity of structural information on these enzymes. The overall goal of this project is to elucidate the mechanism of HDAC function through a combined structure/function approach on a subset of biologically well-characterized HDAC model proteins. The Specific Aims of the proposal are to (1) Characterize the structure/function of the yeast Sir2 homologue, Hst2; (2) Characterize the structure/function of the bacterial Sir2 homologue, CobB; (3) Determine the crystal structure of archaeal Af1-Sir2 bound to its cognate archaeal chromatin protein substrate, Alba; (4) Determine the structure of the archaeal Af1-Sir2 substrate, Alba; (5) Determine the structure of the class I/II HDACs, human HDAC6 and yeast Hos3. Together, these studies will provide new molecular insights into the mode of catalysis and substrate-specific binding by HDACs, as well as the biochemical consequence of HDAC deacetylation. Moreover, these studies will provide a scaffold for the design of small molecule inhibitors for specific histone deacetylase enzymes that may have applications for the treatment of HDAC-mediated cancers.

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- **Project Title: TARGETED LIPOSOMAL DOXORUBICIN DELIVERY TO LEUKEMIA**

  Principal Investigator & Institution: Lee, Robert J.; Associate Professor; None; Ohio State University 1960 Kenny Road Columbus, Oh 43210

  Timing: Fiscal Year 2003; Project Start 01-JUL-2003; Project End 30-JUN-2008

  Summary: (provided by applicant): Targeted drug delivery has the potential to improve the efficacy of a therapeutic agent while reducing its side effects. Folate receptor type-beta (FRB) is a cell surface marker selectively expressed by approximately70 percent of acute myeloid leukemias (AMLs). Increased FR-beta expression can be specifically induced by all trans retinoic acid (ATRA) in FR-beta-positive KG-1 and primary AML cells, without inducing cellular differentiation or growth inhibition. Folic acid is a high

affinity ligand for FR-beta (Kd approximately 1 nM). Importantly, FR-beta expressed by normal hematopoietic cells has been found to be non-functional, whereas the receptor expressed by KG-1 AML cells and FR-beta-transfected CHO cells mediates selective uptake and cytotoxicity of folate-coated liposomes. Both uptake and cytotoxicity of folate coated liposome doxorubicin (f-L-Dox) in KG-1 cells were further increased by ATRA, which induced FR-beta upregulation. Moreover, f-L-DOX exhibited greater therapeutic efficacy than non-targeted liposomal DOX (LDox) in FR positive murine L1210JF and human KG-1 AML ascitic tumor models. Increased survival due to treatment with f-L-Dox was further enhanced by ATRA in the KG-1 engrafted mice. FR-targeted liposomal Dox delivery has also been shown to bypass the P-glycoprotein-mediated drug efflux in FR positive tumor cells exhibiting resistance to free Dox. The objective of this project is to evaluate f-L-Dox, combined with ATRA-induction of FR-beta upregulation, for the treatment of AML, a concept based on the selective targeting of the FR positive tumor cells. The specific aims are: 1. To evaluate the effect of ATRA on FR-beta expression by AML cells in vivo. 2. To evaluate liposome formulation and FR-beta level as factors in the binding and in vitro cytotoxicity of f-L-Dox to AML cells, as well as the pharmacokinetic properties of the liposomes; the effect of dietary folate will also be studied. 3. To evaluate the selective cytotoxicity of f-L-Dox, alone or combined with ATRA, against AML blast cells, clonogenic progenitor cells (CFUs), and primitive AML stem cells (SL-Ics); and 4. To evaluate the in vivo therapeutic efficacy of f-L-Dox alone or combined with ATRA in murine leukemia models. This project should lead to the development of a novel therapeutic strategy based on the combination of targeted drug delivery to tumor cells and upregulation of the cellular target for the treatment of chemotherapy refractory AMLs.

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- **Project Title: TARGETING LIPOSOMAL DAUNORUBICIN TO MYELOID LEUKEMIA**

  Principal Investigator & Institution: Pan, Xing Q.; Sibyl Pharmaceutical, Inc. 2266 St. Roberts Ln Toledo, Oh 43617

  Timing: Fiscal Year 2003; Project Start 22-SEP-2003; Project End 31-AUG-2005

  Summary: (provided by applicant): Targeted drug delivery has the potential to improve the efficacy of a therapeutic agent while reducing its side effects. Folate receptor type-beta (FR-beta) is a cell surface marker selectively expressed by approximately 70% of acute myeloid leukemias (AMLs). Increased FR-beta expression can be specifically induced by all-trans retinoic acid (ATRA) in primary AML cells and in FR-b (+) KG-1 cells, without inducing cellular differentiation or growth inhibition. Folic acid is a high affinity ligand for FR-beta (Kd < 1 nM). Importantly, FR-beta expressed by normal hematopoietic cells cannot bind folate in contrast to that in primary AML cells, KG- 1 cells, and FR-beta-transfected CHO cells, all of which mediate selective uptake and cytotoxicity of folate-coated liposomal doxorubicin (f-L-DOX). FR-beta-targeted uptake and cytotoxicity of f-L-DOX were further enhanced by inducing FR-beta upregulation using ATRA. F-L-DOX also exhibited greater therapeutic efficacy than non-targeted liposomal DOX (L-DOX) in FR (+) murine L1210JF and human KG-1 AML ascitic tumor models. Moreover, ATRA treatment further increased survival in response to treatment with f-L-DOX in the KG-1 cell engrafted SCID mice. FR-targeted liposomal DOX delivery has also been shown to bypass P-glycoprotein-mediated drug efflux in FR (+) tumor cells exhibiting resistance to free DOX. The objective of this Phase I project is to extend and further establish the value of this type of selective targeting using a related but potentially superior anthracycline drug, daunorubicin (DNR) and the superior

NOD/SCID engraftment model. F-L-DNR combined with ATRA, will be evaluated as a therapy for AML using an animal model that more closely mimics human leukemia. The Specific Aims are: 1) to extend a human AML murine NOD/SCID engraftment model to different AML subtypes; 2) to evaluate the effect of ATRA on FR-beta expression by AML cells in the NOD/SCID model; 3) to evaluate the therapeutic efficacy of f-L-DNR, alone or combined with ATRA, in the NOD/SCID model. The data will be used to develop a plan for clinical studies of f-L-DNR/ATRA therapy in a Phase II project.

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- **Project Title: THE ROLE OF CREB IN LEUKEMOGENESIS**

  Principal Investigator & Institution: Sakamoto, Kathleen M.; Pediatrics; University of California Los Angeles 10920 Wilshire Blvd., Suite 1200 Los Angeles, Ca 90024

  Timing: Fiscal Year 2004; Project Start 20-JAN-2004; Project End 31-DEC-2007

  Summary: (provided by applicant): Leukemia is the most common form of childhood cancer. Children with **acute myeloid leukemia** (AML) have less than 50% overall survival despite aggressive chemotherapy and bone marrow transplantation. Therefore, it is critical to understand the molecular pathogenesis of AML. We demonstrated that CREB is overexpressed in bone marrow cells from patients with AML but not in normal bone marrow or bone marrow from patients without active leukemia. Furthermore, CREB overexpression was associated with an increased risk of relapse and decreased event-free survival in patients with AML. Our preliminary results suggest that AML is a heterogeneous disease that is not well understood. We hypothesize that there is an uncoupling of differentiation and CREB expression in myeloid leukemia cells. We propose to study the role of CREB in normal and malignant myeloid cells to identify novel mechanisms of leukemogenesis and improve our understanding of the molecular pathways regulating myeloid cell proliferation and differentiation. In Specific Aim 1, we will characterize CREB expression and activation in primary normal myeloid cells and myeloid leukemia cells. Experiments are proposed to determine the expression of CREB in normal mouse embryos at different stages of hematopoietic development. We will also examine CREB expression in normal myeloid progenitor cells at different stages of myeloid differentiation. Finally, we will examine whether CREB is activated in primary leukemia cells. In Specific Aim 2, we will further characterize the biological phenotype of CREB overexpression and down regulation in myeloid leukemia cell lines and primary normal myeloid cells. Our preliminary results demonstrated that CREB overexpression leads to increased proliferation and survival of myeloid leukemia cells. CREB down regulation using RNA interference (RNAi) suppresses the growth and survival of leukemia cells. To study signaling pathways upstream of CREB, we will overexpress activated kinases and use RNAi technology to inhibit expression of kinases. In Specific Aim 3, we will characterize the phenotype of transgenic mice in which CREB overexpression is targeted to myeloid cells. Defects in hematopoiesis and development of leukemia will be determined in both CREB transgenic mice and a mouse bone marrow transplant model. These studies will define the role of CREB in both normal and malignant myelopoiesis.

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

- **Project Title: THE ROLE OF CYCLIN A1 IN ACUTE MYELOID LEUKEMIA**

  Principal Investigator & Institution: Wolgemuth, Debra J.; Professor; Obstetrics and Gynecology; Columbia University Health Sciences Po Box 49 New York, Ny 10032

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

Summary: (provided by applicant): We have identified a novel mammalian A-type cyclin, cyclin AI, that our targeted mutagenesis in mice revealed to be essential for the progression of male germ cells into meiosis. Human cyclin AI is also highly expressed in myeloid leukemia cell lines and in leukemic cells from patients with acute myeloid leukemias, in the promyelocytic form (APL) in particular. We have tested the hypothesis that the aberrant high levels of cyclin AI were causal in the leukemic phenotype, i.e., acting as an oncogene. Transgenic mice in which cyclin AI was expressed under the control of the human cathepsin G promoter in myeloid precursor cells were generated. They exhibited abnormal myelopoiesis and developed **acute myeloid leukemia** with low penetrance and long latency. Interestingly, in the transgenic mouse model and in human NB4 cells, the localization of cyclin A1 is predominantly cytoplasmic, distinct from its nuclear localization in germ cells. We wish to understand the cellular mechanisms in myelopoiesis that are altered in the presence of elevated levels of cyclin A1 that is now mostly cytoplasmic. The distinct cytoplasmic localization of cyclin A1 will be studied, testing the hypothesis that this property contributes to the tumorigenesis. We will also address the role of cyclin A1 during normal hematopoiesis by studying hematopoietic parameters in mice that are null for the cyclin A1 gene. The hypothesis that cyclin A1 will have distinct Cdk partners, other interacting partners, and substrates in normal versus leukemic cells will be tested using immunoprecipitation and a yeast 2-hybrid screen. As high levels of cyclin A1 protein have been shown to be characteristic of APL, we will ask whether manipulating the expression of cyclin A1 will affect the development of the leukemia. We will test this idea by performing genetic studies in which we will manipulate the expression of cyclin A1 in the fusion oncogene X-RARalpha transgenic animal models of APL. The question is whether these mice will be more resistant to the development of leukemia in the absence of cyclin AI. These studies will provide important insight into the etiology of myeloid leukemia, the role of cell cycle control in the oncogenic process, and the development of new and potentially highly tissue-specific target molecules for pharmacologic intervention.

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- **Project Title: THE ROLE OF MOZ IN NORMAL AND LEUKEMIC HEMATOPOIESIS**

  Principal Investigator & Institution: Snyder, Cynthia S.; Cellular & Molecular Medicine; University of California San Diego La Jolla, Ca 920930934

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

  Summary: (provided by applicant) Differentiating hematopoietic progenitors demonstrate an orderly maturation of chromatin, a progression that provides distinctive morphologic cues as to a cell's identity and stage of maturity. These nuclear changes, visible under the light microscope, mirror the changes in gene expression that hematopoietic stem cells undergo as they differentiate towards the various mature hematopoietic lineages. However, it is becoming increasingly clear that changes in chromatin structure do not merely reflect the molecular decision making of transcription factors and the signaling pathways to which they respond. Rather, changes directed at chromatin remodeling help to determine global patterns of gene expression, patterns which can be inherited and enhanced with each cell cycle. Many important hematopoietic regulators have been identified due to their involvement in leukemia-associated chromosomal translocations. The MOZ gene, situated at chromosomal band 8p1l, is involved in three independent myeloid leukemia translocations. MOZ partner genes disrupted by t(8;16), t(8;22), and inv(8) are, respectively, the CREB binding protein (CBP) at 16p13, P300 at 22q13, and TIF2 (NCoA-2) at 8q13; all three partners are histone

acetyltransferases and nuclear receptor coregulators. MOZ is a putative histone acetyltransferase (HAT) and the founding member of the MYST family of HATs, a family that includes proteins involved in cell cycle regulation, chromatin remodeling, and dosage compensation. MOZ's structure suggests that, like CBP/P300 and other members of the HAT superfamily, MOZ participates in protein complexes that modulate both transcriptional activity and chromatin structure. This proposal tests the hypothesis that MOZ is a histone acetyltransferase and transcriptional coregulator that plays an important role during hematopoiesis. Disruption of the MOZ gene by chromosomal translocations is proposed to interfere with critical hematopoietic signaling pathways, disrupt myelopoiesis, and contribute to the development of **acute myeloid leukemia.** The specific aims of this proposal are to 1) characterize MOZ expression during embryonic development, hematopoiesis, and the cell cycle using northern blotting, western blotting, in situ hybridization, and immunohistochemistry; 2) assess MOZ's coregulatory functions, and its dependence on an intact acetyltransferase activity, using transient and retroviral-mediated stable transfection assays and microinjection studies in hematopoietic and non-hematopoietic cells; and 3) define how disruption of the normal functions of MOZ affects murine embryonic development and hematopoiesis using targeted disruption of the MOZ gene. The long term goal of this project is to understand how MOZ contributes to commitment and terminal differentiation during hematopoiesis.

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- **Project Title: THERAPY OF LYMPHOMA/LEUKEMIA WITH MONOCLONAL ANTIBODIES**

  Principal Investigator & Institution: Press, Oliver W.; Professor of Medicine; Fred Hutchinson Cancer Research Center Box 19024, 1100 Fairview Ave N Seattle, Wa 98109

  Timing: Fiscal Year 2002; Project Start 01-JUN-1988; Project End 30-APR-2005

  Summary: The overall goal of this program project is to develop effective strategies for treating patients with hematologic malignancies using radiolabeled monoclonal antibodies in conjunction with stem cell transplantation. Our studies have established the feasibility and anti-tumor activity of this approach and have led us to focus on several critical issues. The first is to fully establish The first is to fully establish the efficacy of our approach in extended Phase II trials and provide a basis for Phase III comparisons to conventional approaches. The second is to apply these approaches in patients not tolerant of current maximal dose therapies but who may benefit from a targeted therapy approach. The third is to improve the relative delivery of radiation to tumor compared to normal organs, an area critical for advancing this therapeutic modality. Thus, in Projects I and II, we will continue our Phase II trials, of radiolabeled antibody combined for patients with relapsed lymphoma or **acute myeloid leukemia** (AML) and myelodysplastic syndrome (MDS), and determine a basis for proceeding to definitive Phase III randomized trials. In elderly patients with lymphoma, we will investigate the feasibility and efficacy of administering single agent high-dose I-131-labeled anti-B-cell antibody and stem cell transplantation, and in elderly patients with advanced AML, we will investigate radiation delivered via I-131-anti-CD45 antibody combined with a low-dose, non-myeloablative regimen prior to matched related stem cell infusion. To improve delivery of radiation, in Project III we propose a novel approach a novel approach based on the rapid removal of circulating non-tumor bound radioisotope to decrease the radiation delivered to normal organs and improve the relative deliver of radiation to the tumor compared to those organs.

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

- **Project Title: TYROSINE KINASE ONCOGENESIS IN MYELOID LEUKEMIA**

  Principal Investigator & Institution: Griffin, James D.; Professor; Dana-Farber Cancer Institute 44 Binney St Boston, Ma 02115

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

  Summary: (provided by applicant): The long-term goals of this Program are to understand the pathogenesis of acute myeloid leukemias and use this information to develop novel therapeutic strategies to cure these disorders. A central hypothesis is that AML's are caused by multiple oncogenes that cooperate to cause leukemia. Thus, different leukemia oncogenes are likely to disrupt various cellular processes. An essential event is blocking differentiation, most likely by disrupting the transcription factor network that regulates myelopoiesis. The focus of this project is to understand the contribution of mutations in FLT3 to the pathogenesis of AML, and use this information to develop novel therapeutic strategies. FLT3 is a tyrosine kinase transmembrane receptor normally expressed in immature myeloid cells and required for proper development of hematopoietic stem cells, B cells, dendritic cells, and NK cells. Mutations in this receptor have been discovered in 20-30% of AMLs and are believed to cause constitutive activation of the receptor. Most of the mutations are in the juxtamembrane domain immediately inside the cell membrane, and involve in-frame, tandem, duplications of usually short stretches of DNA. In this project, we will determine the mechanism whereby these JM domain duplications activate the receptor, examine the mechanism of activation of a point mutation that also activates the receptor (D835Y), and compare the transforming functions of mutant FLT3 to those of another common tyrosine kinase oncogene of myeloid leukemias, BCR/ABL. Finally, small molecule kinase inhibitors are now available for both FLT3 and BCR/ABL and they will be studied to determine mechanisms of action on leukemic cells, modes of resistance, and opportunities for incorporation into novel combination chemotherapies. Successful completion of the studies proposed in this project will result in improved understanding of the pathogenesis of AML and the development of novel treatment strategies.

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

- **Project Title: ZEBRAFISH MODELS OF FLT3-MEDIATED MYELOID LEUKEMIAS**

  Principal Investigator & Institution: Hsu, Karl; Dana-Farber Cancer Institute 44 Binney St Boston, Ma 02115

  Timing: Fiscal Year 2002; Project Start 01-AUG-2002; Project End 30-JUN-2007

  Summary: (provided by applicant): This proposal is designed to merge the candidate's background in molecular biology and clinical experience in hematology/oncology to produce an independent physician-scientist investigator. Dr. A. Thomas Look, the candidate's mentor, is a recognized leader in leukemia research and has committed major resources at the Dana-Farber Cancer Institute to use the zebrafish as a model to study human myeloid cell development. In addition, an advisory committee of highly regarded medical scientists will provide scientific and career advice. The goal of this application is to use the genetic and embryonic advantages of the zebrafish to determine the pathophysiologic significance in hematopoiesis and leukemia of constitutive activating mutations in the class III receptor tyrosine kinase FLT3 gene, which is mutated in 20-30% of **acute myeloid leukemia** (AML) patients. The central hypothesis is that AMLs are caused by the synergistic action of specific classes of mutations acting in tandem. These include, first, an activated tyrosine kinase gene for stimulation of growth/survival (Class I) and, second, either in activation of a gene required for normal myeloid differentiation or activation of a chimeric transcription factor oncogene that can

produce a block of myeloid cell development (Class II). Dr. Hsu will define the spectrum of phenotypes, including a potential proliferative and survival advantage, induced by constitutive expression of the FLT3-ITD tyrosine kinase mutant in developing zebrafish myeloid cells (Aim #l). He will also establish stable transgenic lines of zebrafish that over-express FLT3-ITD in myeloid stem and progenitor cells and monitor these fish for the development of myeloproliferative syndrome and AML (Aim #2). The development of stable transgenic lines is critical for testing the central hypothesis. These stable lines are also vital for the investigator's future goal of conducting modifier screens to discover additional important genes in the hematopoietic pathways used by the activated FLT3 kinase. Insight into this pathway may lead to discovery of shared components of the pathway in the 60 to 70 percent of AMLs that do not have a FLT3 mutation and the identification of genes that can serve as potential drug targets.

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

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 "acute myeloid leukemia" (or synonyms) into the search box. This search gives you access to full-text articles. The following is a sample of items found for acute myeloid leukemia in the PubMed Central database:

- **A pilot study of high-throughput, sequence-based mutational profiling of primary human acute myeloid leukemia cell genomes.** by Ley TJ, Minx PJ, Walter MJ, Ries RE, Sun H, McLellan M, DiPersio JF, Link DC, Tomasson MH, Graubert TA, McLeod H, Khoury H, Watson M, Shannon W, Trinkaus K, Heath S, Vardiman JW, Caligiuri MA, Bloomfield CD, Milbrandt JD, Mardis ER, Wilson RK.; 2003 Nov 25; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=283582
- **Aberrant Recruitment of the Nuclear Receptor Corepressor-Histone Deacetylase Complex by the Acute Myeloid Leukemia Fusion Partner ETO.** by Gelmetti V, Zhang J, Fanelli M, Minucci S, Pelicci PG, Lazar MA.; 1998 Dec; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=109300
- **Acute myeloid leukemia fusion proteins deregulate genes involved in stem cell maintenance and DNA repair.** by Alcalay M, Meani N, Gelmetti V, Fantozzi A, Fagioli M, Orleth A, Riganelli D, Sebastiani C, Cappelli E, Casciari C, Sciurpi MT, Mariano AR, Minardi SP, Luzi L, Muller H, Di Fiore PP, Frosina G, Pelicci PG.; 2003 Dec 1; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=281638

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[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.

- **Acute myeloid leukemia induction by amphotropic murine retrovirus (4070A): clonal integrations involve c-myb in some but not all leukemias.** by Wolff L, Koller R, Davidson W.; 1991 Jul;
  http://www.pubmedcentral.gov/picrender.fcgi?tool=pmcentrez&action=stream&blobtype=pdf&artid=241365
- **Acute myeloid leukemias with reciprocal rearrangements can be distinguished by specific gene expression profiles.** by Schoch C, Kohlmann A, Schnittger S, Brors B, Dugas M, Mergenthaler S, Kern W, Hiddemann W, Eils R, Haferlach T.; 2002 Jul 23;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=126615
- **Altered myelopoiesis and the development of acute myeloid leukemia in transgenic mice overexpressing cyclin A1.** by Liao C, Wang XY, Wei HQ, Li SQ, Merghoub T, Pandolfi PP, Wolgemuth DJ.; 2001 Jun 5;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=34442
- **Alternative splicing and genomic structure of the AML1 gene involved in acute myeloid leukemia.** by Miyoshi H, Ohira M, Shimizu K, Mitani K, Hirai H, Imai T, Yokoyama K, Soeda E, Ohki M.; 1995 Jul 25;
  http://www.pubmedcentral.gov/picrender.fcgi?tool=pmcentrez&action=stream&blobtype=pdf&artid=307102
- **AML1-ETO expression is directly involved in the development of acute myeloid leukemia in the presence of additional mutations.** by Yuan Y, Zhou L, Miyamoto T, Iwasaki H, Harakawa N, Hetherington CJ, Burel SA, Lagasse E, Weissman IL, Akashi K, Zhang DE.; 2001 Aug 28;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=56972
- **An activated receptor tyrosine kinase, TEL/PDGF[beta]R, cooperates with AML1/ETO to induce acute myeloid leukemia in mice.** by Grisolano JL, O'Neal J, Cain J, Tomasson MH.; 2003 Aug 5;
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- **Analysis of RAS gene mutations in acute myeloid leukemia by polymerase chain reaction and oligonucleotide probes.** by Farr CJ, Saiki RK, Erlich HA, McCormick F, Marshall CJ.; 1988 Mar;
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- **CD8 + minor histocompatibility antigen-specific cytotoxic T lymphocyte clones eliminate human acute myeloid leukemia stem cells.** by Bonnet D, Warren EH, Greenberg PD, Dick JE, Riddell SR.; 1999 Jul 20;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=17569
- **Cloning of ELL, a gene that fuses to MLL in a t(11;19)(q23;p13.1) in acute myeloid leukemia.** by Thirman MJ, Levitan DA, Kobayashi H, Simon MC, Rowley JD.; 1994 Dec 6;
  http://www.pubmedcentral.gov/picrender.fcgi?tool=pmcentrez&action=stream&blobtype=pdf&artid=45386
- **Core Binding Factor [beta]--Smooth Muscle Myosin Heavy Chain Chimeric Protein Involved in Acute Myeloid Leukemia Forms Unusual Nuclear Rod-Like Structures in Transformed NIH 3T3 Cells.** by Wijmenga C, Gregory PE, Hajra A, Schrock E, Ried T, Eils R, Liu PP, Collins FS.; 1996 Feb 20;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&rendertype=abstract&artid=39993

- **Defining Roles for HOX and MEIS1 Genes in Induction of Acute Myeloid Leukemia.** by Thorsteinsdottir U, Kroon E, Jerome L, Blasi F, Sauvageau G.; 2001 Jan 1; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=88796
- **E2A-Pbx1, the t(1;19) translocation protein of human pre-B-cell acute lymphocytic leukemia, causes acute myeloid leukemia in mice.** by Kamps MP, Baltimore D.; 1993 Jan; http://www.pubmedcentral.gov/picrender.fcgi?tool=pmcentrez&action=stream&blobtype=pdf&artid=358914
- **Erythematous eruption in a man with acute myeloid leukemia.** by Tay J.; 2002 Sep 17; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=122036
- **ETO, fusion partner in t(8;21) acute myeloid leukemia, represses transcription by interaction with the human N-CoR/mSin3/HDAC1 complex.** by Wang J, Hoshino T, Redner RL, Kajigaya S, Liu JM.; 1998 Sep 1; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=27986
- **Expression of the Human Acute Myeloid Leukemia Gene AML1 is Regulated by Two Promoter Regions.** by Ghozi MC, Bernstein Y, Negreanu V, Levanon D, Groner Y.; 1996 Mar 5; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&rendertype=abstract&artid=39886
- **Expression profiling of CD34 + hematopoietic stem / progenitor cells reveals distinct subtypes of therapy-related acute myeloid leukemia.** by Qian Z, Fernald AA, Godley LA, Larson RA, Le Beau MM.; 2002 Nov 12; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=137521
- **Expression profiling reveals fundamental biological differences in acute myeloid leukemia with isolated trisomy 8 and normal cytogenetics.** by Virtaneva K, Wright FA, Tanner SM, Yuan B, Lemon WJ, Caligiuri MA, Bloomfield CD, de la Chapelle A, Krahe R.; 2001 Jan 30; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=14719
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- **Growth inhibition and induction of differentiation of t(8;21) acute myeloid leukemia cells by the DNA-binding domain of PEBP2 and the AML1/MTG8(ETO)-specific antisense oligonucleotide.** by Sakakura C, Yamaguchi-Iwai Y, Satake M, Bae SC, Takahashi A, Ogawa E, Hagiwara A, Takahashi T, Murakami A, Makino K, et al.; 1994 Nov 22; http://www.pubmedcentral.gov/picrender.fcgi?tool=pmcentrez&action=stream&blobtype=pdf&artid=45304
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- **Identification of a gene at 11q23 encoding a guanine nucleotide exchange factor: Evidence for its fusion with MLL in acute myeloid leukemia.** by Kourlas PJ, Strout MP, Becknell B, Veronese ML, Croce CM, Theil KS, Krahe R, Ruutu T, Knuutila S, Bloomfield CD, Caligiuri MA.; 2000 Feb 29; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=15768

- **Interleukin 1 as an autocrine growth factor for acute myeloid leukemia cells.** by Cozzolino F, Rubartelli A, Aldinucci D, Sitia R, Torcia M, Shaw A, Di Guglielmo R.; 1989 Apr;
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- **MLL is fused to CBP, a histone acetyltransferase, in therapy-related acute myeloid leukemia with a t(11;16)(q23;p13.3).** by Sobulo OM, Borrow J, Tomek R, Reshmi S, Harden A, Schlegelberger B, Housman D, Doggett NA, Rowley JD, Zeleznik-Le NJ.; 1997 Aug 5;
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- **NUP98 --HOXA9 expression in hemopoietic stem cells induces chronic and acute myeloid leukemias in mice.** by Kroon E, Thorsteinsdottir U, Mayotte N, Nakamura T, Sauvageau G.; 2001 Feb 1;
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- **Overexpression of HOXA10 in murine hematopoietic cells perturbs both myeloid and lymphoid differentiation and leads to acute myeloid leukemia.** by Thorsteinsdottir U, Sauvageau G, Hough MR, Dragowska W, Lansdorp PM, Lawrence HJ, Largman C, Humphries RK.; 1997 Jan;
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- **Retroviral Integration at the Epi1 Locus Cooperates with Nf1 Gene Loss in the Progression to Acute Myeloid Leukemia.** by Blaydes SM, Kogan SC, Truong BT, Gilbert DJ, Jenkins NA, Copeland NG, Largaespada DA, Brannan CI.; 2001 Oct 1;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=114510
- **Retrovirus-mediated gene transfer of MLL-ELL transforms primary myeloid progenitors and causes acute myeloid leukemias in mice.** by Lavau C, Luo RT, Du C, Thirman MJ.; 2000 Sep 26;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=27135
- **Subcellular localization of the alpha and beta subunits of the acute myeloid leukemia-linked transcription factor PEBP2/CBF.** by Lu J, Maruyama M, Satake M, Bae SC, Ogawa E, Kagoshima H, Shigesada K, Ito Y.; 1995 Mar;
  http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&rendertype=abstract&artid=230389
- **Surface expression and function of p75/AIRM-1 or CD33 in acute myeloid leukemias: Engagement of CD33 induces apoptosis of leukemic cells.** by Vitale C, Romagnani C, Puccetti A, Olive D, Costello R, Chiossone L, Pitto A, Bacigalupo A, Moretta L, Mingari MC.; 2001 May 8;
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- **t(11;22)(q23;q11.2) in acute myeloid leukemia of infant twins fuses MLL with hCDCrel, a cell division cycle gene in the genomic region of deletion in DiGeorge and velocardiofacial syndromes.** by Megonigal MD, Rappaport EF, Jones DH, Williams TM, Lovett BD, Kelly KM, Lerou PH, Moulton T, Budarf ML, Felix CA.; 1998 May 26; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=27754
- **t(8;21) breakpoints on chromosome 21 in acute myeloid leukemia are clustered within a limited region of a single gene, AML1.** by Miyoshi H, Shimizu K, Kozu T, Maseki N, Kaneko Y, Ohki M.; 1991 Dec 1; http://www.pubmedcentral.gov/picrender.fcgi?tool=pmcentrez&action=stream&blobtype=pdf&artid=52942
- **Telomere-like DNA polymorphisms associated with genetic predisposition to acute myeloid leukemia in irradiated CBA mice.** by Silver A, Cox R.; 1993 Feb 15; http://www.pubmedcentral.gov/picrender.fcgi?tool=pmcentrez&action=stream&blobtype=pdf&artid=45882
- **The ETO Protein Disrupted in t(8;21)-Associated Acute Myeloid Leukemia Is a Corepressor for the Promyelocytic Leukemia Zinc Finger Protein.** by Melnick AM, Westendorf JJ, Polinger A, Carlile GW, Arai S, Ball HJ, Lutterbach B, Hiebert SW, Licht JD.; 2000 Mar 15; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=110824
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- **The human GRAF gene is fused to MLL in a unique t(5;11)(q31;q23) and both alleles are disrupted in three cases of myelodysplastic syndrome /acute myeloid leukemia with a deletion 5q.** by Borkhardt A, Bojesen S, Haas OA, Fuchs U, Bartelheimer D, Loncarevic IF, Bohle RM, Harbott J, Repp R, Jaeger U, Viehmann S, Henn T, Korth P, Scharr D, Lampert F.; 2000 Aug 1; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=16840
- **The inv(16) encodes an acute myeloid leukemia 1 transcriptional corepressor.** by Lutterbach B, Hou Y, Durst KL, Hiebert SW.; 1999 Oct 26; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=23113
- **The partial tandem duplication of ALL1 (MLL) is consistently generated by Alu-mediated homologous recombination in acute myeloid leukemia.** by Strout MP, Marcucci G, Bloomfield CD, Caligiuri MA.; 1998 Mar 3; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=19353
- **The partial tandem duplication of ALL1 in acute myeloid leukemia with normal cytogenetics or trisomy 11 is restricted to one chromosome.** by Caligiuri MA, Strout MP, Oberkircher AR, Yu F, de la Chapelle A, Bloomfield CD.; 1997 Apr 15; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=20539
- **Therapeutic targeting of the MEK/MAPK signal transduction module in acute myeloid leukemia.** by Milella M, Kornblau SM, Estrov Z, Carter BZ, Lapillonne H, Harris D, Konopleva M, Zhao S, Estey E, Andreeff M.; 2001 Sep 15; http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=200930

- **Tumor necrosis factor downregulates granulocyte-colony-stimulating factor receptor expression on human acute myeloid leukemia cells and granulocytes.** by Elbaz O, Budel LM, Hoogerbrugge H, Touw IP, Delwel R, Mahmoud LA, Lowenberg B.; 1991 Mar;
  http://www.pubmedcentral.gov/picrender.fcgi?tool=pmcentrez&action=stream&blobtype=pdf&artid=329871

The National Library of Medicine: PubMed

One of the quickest and most comprehensive ways to find academic studies in both English and other languages is to use PubMed, maintained by the National Library of Medicine.[6] The advantage of PubMed over previously mentioned sources is that it covers a greater number of domestic and foreign references. It is also free to use. If the publisher has a Web site that offers full text of its journals, PubMed will provide links to that site, as well as to sites offering other related data. User registration, a subscription fee, or some other type of fee may be required to access the full text of articles in some journals.

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

- **A phase 2 clinical study of SU5416 in patients with refractory acute myeloid leukemia.**
  Author(s): Fiedler W, Mesters R, Tinnefeld H, Loges S, Staib P, Duhrsen U, Flasshove M, Ottmann OG, Jung W, Cavalli F, Kuse R, Thomalla J, Serve H, O'Farrell AM, Jacobs M, Brega NM, Scigalla P, Hossfeld DK, Berdel WE.
  Source: Blood. 2003 October 15; 102(8): 2763-7. Epub 2003 July 03.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12843001

- **A pilot study of high-throughput, sequence-based mutational profiling of primary human acute myeloid leukemia cell genomes.**
  Author(s): Ley TJ, Minx PJ, Walter MJ, Ries RE, Sun H, McLellan M, DiPersio JF, Link DC, Tomasson MH, Graubert TA, McLeod H, Khoury H, Watson M, Shannon W, Trinkaus K, Heath S, Vardiman JW, Caligiuri MA, Bloomfield CD, Milbrandt JD, Mardis ER, Wilson RK.
  Source: Proceedings of the National Academy of Sciences of the United States of America. 2003 November 25; 100(24): 14275-80. Epub 2003 Nov 12.
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[6] PubMed was developed by the National Center for Biotechnology Information (NCBI) at the National Library of Medicine (NLM) at the National Institutes of Health (NIH). The PubMed database was developed in conjunction with publishers of biomedical literature as a search tool for accessing literature citations and linking to full-text journal articles at Web sites of participating publishers. Publishers that participate in PubMed supply NLM with their citations electronically prior to or at the time of publication.

- **Aberrant expression of HOXA9, DEK, CBL and CSF1R in acute myeloid leukemia.**
  Author(s): Casas S, Nagy B, Elonen E, Aventin A, Larramendy ML, Sierra J, Ruutu T, Knuutila S.
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- **Abundant expression of fibronectin is a major feature of leukemic dendritic cells differentiated from patients with acute myeloid leukemia.**
  Author(s): Vialle-Castellano A, Gaugler B, Mohty M, Isnardon D, van Baren N, Olive D.
  Source: Leukemia : Official Journal of the Leukemia Society of America, Leukemia Research Fund, U.K. 2004 March; 18(3): 426-33.
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  Author(s): Shih LY, Huang CF, Wang PN, Wu JH, Lin TL, Dunn P, Kuo MC.
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- **Acute monocytic leukemia (French-American-British classification M5) does not have a worse prognosis than other subtypes of acute myeloid leukemia: a report from the Eastern Cooperative Oncology Group.**
  Author(s): Tallman MS, Kim HT, Paietta E, Bennett JM, Dewald G, Cassileth PA, Wiernik PH, Rowe JM; Eastern Cooperative Oncology Group.
  Source: Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology. 2004 April 1; 22(7): 1276-86. Epub 2004 February 17.
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- **Acute myeloid leukemia cells in G0 phase of the cell cycle that are unresponsive to conventional chemotherapy are sensitive to treatment with granulocyte-macrophage colony-stimulating factor/diphtheria toxin fusion proteins.**
  Author(s): Jedema I, Barge RM, Frankel AE, Willemze R, Falkenburg JH.
  Source: Experimental Hematology. 2004 February; 32(2): 188-94.
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  Author(s): Alcalay M, Meani N, Gelmetti V, Fantozzi A, Fagioli M, Orleth A, Riganelli D, Sebastiani C, Cappelli E, Casciari C, Sciurpi MT, Mariano AR, Minardi SP, Luzi L, Muller H, Di Fiore PP, Frosina G, Pelicci PG.
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- **Acute myeloid leukemia in elderly patients: experience of a single center.**
  Author(s): Rodrigues CA, Chauffaille ML, Pelloso LA, Ghaname FS, Kerbauy DM, Campos MG, Yamamoto M.
  Source: Brazilian Journal of Medical and Biological Research = Revista Brasileira De Pesquisas Medicas E Biologicas / Sociedade Brasileira De Biofisica. [et Al.]. 2003 June; 36(6): 703-8. Epub 2003 June 03.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12792698

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  Author(s): Rajput R, Marwah N, Chitkara N, Singh S, Meena.
  Source: Indian J Pathol Microbiol. 2003 July; 46(3): 535-6. No Abstract Available.
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  Author(s): Chen E, Morrison DG, Donahue SP.
  Source: American Journal of Ophthalmology. 2004 May; 137(5): 948-50.
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  Source: Indian Pediatrics. 2003 December; 40(12): 1191-4.
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  Author(s): Breccia M, Gentile G, Martino P, Petti MC, Russo E, Mancini M, Alimena G.
  Source: Acta Haematologica. 2004; 111(3): 160-2.
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  Author(s): Baldus CD, Liyanarachchi S, Mrozek K, Auer H, Tanner SM, Guimond M, Ruppert AS, Mohamed N, Davuluri RV, Caligiuri MA, Bloomfield CD, de la Chapelle A.
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- **Addition of cladribine to daunorubicin and cytarabine increases complete remission rate after a single course of induction treatment in acute myeloid leukemia. Multicenter, phase III study.**
  Author(s): Holowiecki J, Grosicki S, Robak T, Kyrcz-Krzemien S, Giebel S, Hellmann A, Skotnicki A, Jedrzejczak WW, Konopka L, Kuliczkowski K, Zdziarska B, Dmoszynska A, Marianska B, Pluta A, Zawilska K, Komarnicki M, Kloczko J, Sulek K, Haus O, Stella-Holowiecka B, Baran W, Jakubas B, Paluszewska M, Wierzbowska A, Kielbinski M, Jagoda K; Polish Adult Leukemia Group (PALG).
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CHAPTER 2. NUTRITION AND ACUTE MYELOID LEUKEMIA

Overview

In this chapter, we will show you how to find studies dedicated specifically to nutrition and acute myeloid leukemia.

Finding Nutrition Studies on Acute Myeloid Leukemia

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 "acute myeloid leukemia" (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 "acute myeloid leukemia" (or a synonym):

- **A phase I study of induction chemotherapy for older patients with newly diagnosed acute myeloid leukemia (AML) using mitoxantrone, etoposide, and the MDR modulator PSC 833: a southwest oncology group study 9617.**
  Author(s): University of Washington School of Medicine, Seattle, WA, USA.
  Source: Chauncey, T R Rankin, C Anderson, J E Chen, I Kopecky, K J Godwin, J E Kalaycio, M E Moore, D F Shurafa, M S Petersdorf, S H Kraut, E H Leith, C P Head, D R Luthardt, F W Willman, C L Appelbaum, F R Leuk-Res. 2000 July; 24(7): 567-74 0145-2126

- **A phase I/II study of intensive dose escalation of cytarabine in combination with idarubicin and etoposide in induction and consolidation treatment of adult acute myeloid leukemia. Australian Leukaemia Study Group (ALSG).**
  Author(s): Haematology/Oncology Unit, Royal Hobart Hospital, Tasmania, Australia. R.M.Lowenthal@utas.edu.au
  Source: Lowenthal, R M Bradstock, K F Matthews, J P Bishop, J F Juneja, S Cobcroft, R Eliadis, P Enno, A Gill, D Herrmann, R P Manoharan, A Page, F J Rooney, K F Rosenfeld, D Seldon, M Taylor, K M Wolf, M M Young, G A Leuk-Lymphoma. 1999 August; 34(5-6): 501-10 1042-8194

- **Acute promyelocytic leukemia relapsing into FAB-M2 acute myeloid leukemia with trisomy 8.**
  Author(s): First Department of Medicine, University of Athens, Greece.
  Source: Stavroyianni, N Yataganas, X Abazis, D Pangalos, C Meletis, J Cancer-Genet-Cytogenet. 2000 February; 117(1): 82-3 0165-4608

- **Adenosine analogs as possible differentiation-inducing agents against acute myeloid leukemia.**
  Author(s): Department of Chemotherapy, Saitama Cancer Center Research Institute, Japan.
  Source: Niitsu, N Honma, Y Leuk-Lymphoma. 1999 July; 34(3-4): 261-71 1042-8194

- **Autologous bone marrow transplantation for acute myeloid leukemia using 4-hydroperoxycyclophosphamide-purged bone marrow and the busulfan/etoposide preparative regimen: a follow-up report.**
  Author(s): University of California San Francisco, USA.
  Source: Linker, C A Ries, C A Damon, L E Rugo, H S Wolf, J L Bone-Marrow-Transplant. 1998 November; 22(9): 865-72 0268-3369

- **Autologous stem cell transplantation for acute myeloid leukemia in first remission.**
  Author(s): University of California, San Francisco, USA. linkerc@medicine.ucsf.edu
  Source: Linker, C A Ries, C A Damon, L E Sayre, P Navarro, W Rugo, H S Rubin, A Case, D Crilley, P Topolsky, D Brodsky, I Zamkoff, K Wolfe, J L Biol-Blood-Marrow-Transplant. 2000; 6(1): 50-7 1083-8791

- **Combination of topotecan with cytarabine or etoposide in patients with refractory or relapsed acute myeloid leukemia: results of a randomized phase I/II study.**
  Author(s): Leukemia Department, University of Texas, M.D. Anderson Cancer Center, Houston 77030, USA.
  Source: Vey, N Kantarjian, H Beran, M O'Brien, S Cortes, J Koller, C Estey, E Invest-New-Drugs. 1999; 17(1): 89-95 0167-6997

- **Cyclosporine-induced autologous graft-versus-host disease in patients with acute myeloid leukemia undergoing non-myeloablative chemotherapy without progenitor cell reinfusion.**
  Author(s): New York Medical College, New York, NY, USA.
  Source: Stein, M Feldman, E Seiter, K Chiao, J W Goff, H Baskind, P Beer, M Ahmed, T Bone-Marrow-Transplant. 1999 November; 24(10): 1073-7 0268-3369

- **Cytotoxicity of anti-CD64-ricin a chain immunotoxin against human acute myeloid leukemia cells in vitro and in SCID mice.**
  Author(s): Department of Medicine, and the Cancer Center, University of California, San Diego, La Jolla, CA 92093, USA.
  Source: Zhong, R K van de Winkel, J G Thepen, T Schultz, L D Ball, E D J-Hematother-Stem-Cell-Res. 2001 February; 10(1): 95-105 1525-8165

- **Donor cell-derived acute myeloid leukemia developing 14 months after matched unrelated bone marrow transplantation for chronic myeloid leukemia.**
  Author(s): Department of Hematology and Oncology, Hannover Medical School, Carl-Neuberg-Strasse 1, 30625 Hannover, Germany.
  Source: Hambach, L Eder, M Dammann, E Battmer, K Stucki, A Heil, G Ganser, A Hertenstein, B Bone-Marrow-Transplant. 2001 October; 28(7): 705-7 0268-3369

- **Expression of the 67-kDa laminin receptor in acute myeloid leukemia cells mediates adhesion to laminin and is frequently associated with monocytic differentiation.**
  Author(s): Department of Cellular and Molecular Biology and Pathology, Federico II University Medical School, Naples, Italy.
  Source: Montuori, N Selleri, C Risitano, A M Raiola, A M Ragno, P Del Vecchio, L Rotoli, B Rossi, G Clin-Cancer-Res. 1999 June; 5(6): 1465-72 1078-0432

- **Granulocyte colony-stimulating factor after intensive consolidation chemotherapy in acute myeloid leukemia: results of a randomized trial of the Groupe Ouest-Est Leucemies Aigues Myeloblastiques.**
  Author(s): Departments of Hematology of University Hospital, Nantes, France. jlharousseau@sante.univ_nantes.fr
  Source: Harousseau, J L Witz, B Lioure, B Hunault Berger, M Desablens, B Delain, M Guilhot, F Le Prise, P Y Abgrall, J F Deconinck, E Guyotat, D Vilque, J P Casassus, P Tournilhac, O Audhuy, B Solary, E J-Clin-Oncol. 2000 February; 18(4): 780-7 0732-183X

- **High-dose melphalan with autologous hematopoietic stem cell transplantation for acute myeloid leukemia: results of a retrospective analysis of the Italian Pediatric Group for Bone Marrow Transplantation.**
  Author(s): Clinica di Oncoematologia Pediatrica, Dipartimento di Pediatria, Universita di Padova, Italy.
  Source: Cesaro, S Meloni, G Messina, C Pillon, M Proglia, A Lanino, E Caniggia, M Bagnulo, S Pession, A Locatelli, F Bone-Marrow-Transplant. 2001 July; 28(2): 131-6 0268-3369

- **Impact of exogenous growth factors on proliferation and chemosensitivity of minimal residual acute myeloid leukemia.**
  Author(s): The Johns Hopkins Oncology Center, Baltimore, Maryland, USA. sdgore@welchlink.welch.jhu.edu
  Source: Gore, S D Burke, P J Weng, L J Leuk-Lymphoma. 1998 April; 29(3-4): 339-50 1042-8194

- **Impact of the expression of P glycoprotein, the multidrug resistance-related protein, bcl-2, mutant p53, and heat shock protein 27 on response to induction therapy and long-term survival in patients with de novo acute myeloid leukemia.**
  Author(s): Departments of Internal Medicine (Cancer Research), University of Essen, Medical School, West German Cancer Center, Essen, Germany. sabine.kasimir-bauer@uni-essen.de
  Source: Kasimir Bauer, S Beelen, D Flasshove, M Noppeney, R Seeber, S Scheulen, M E Exp-Hematol. 2002 November; 30(11): 1302-8 0301-472X

- **Intensified induction chemotherapy with high dose cytarabine and etoposide for acute myeloid leukemia: a review and updated results of the Australian Leukemia Study Group.**
  Author(s): Sydney Cancer Center, Royal Prince, Alfred Hospital, University of Sydney, NSW, Australia. jbishop@canc.rpa.cs.nsw.gov.au
  Source: Bishop, J F Matthews, J P Young, G A Bradstock, K Lowenthal, R M Leuk-Lymphoma. 1998 January; 28(3-4): 315-27 1042-8194

- **Intensive chemotherapy with idarubicin, ara-C, etoposide, and m-AMSA followed by immunotherapy with interleukin-2 for myelodysplastic syndromes and high-risk Acute Myeloid Leukemia (AML).**
  Author(s): Medizinische Klinik III, Klinikum der Universitat Frankfurt, Germany.
  Source: Ganser, A Heil, G Seipelt, G Hofmann, W Fischer, J T Langer, W Brockhaus, W Kolbe, K Ittel, T H Brack, N Fuhr, H G Knuth, P Hoffken, K Bergmann, L Hoelzer, D Ann-Hematol. 2000 January; 79(1): 30-5 0939-5555

- **Intracellular markers in acute myeloid leukemia diagnosis.**
  Author(s): Cancer Research Institute, Slovak Academy of Sciences, Bratislava, Slovakia.
  Source: Konikova, E Glasova, M Kusenda, J Babusikova, O Neoplasma. 1998; 45(5): 282-91 0028-2685

- **Inversion of chromosome 16 and uncommon rearrangements of the CBFB and MYH11 genes in therapy-related acute myeloid leukemia: rare events related to DNA-topoisomerase II inhibitors?**
  Author(s): Laboratory for Cancer Genetics and Cytogenetics, The Finsen Center, Rigshospitalet, Copenhagen, Denmark.
  Source: Dissing, M Le Beau, M M Pedersen Bjergaard, J J-Clin-Oncol. 1998 May; 16(5): 1890-6 0732-183X

- **Late effects of chemotherapy compared to bone marrow transplantation in the treatment of pediatric acute myeloid leukemia and myelodysplasia.**
  Author(s): Department of Pediatrics, The Children's Hospital of Philadelphia, University of Pennsylvania, 19104, USA. leahey@kermit.oncol.chop.edu
  Source: Leahey, A M Teunissen, H Friedman, D L Moshang, T Lange, B J Meadows, A T Med-Pediatr-Oncol. 1999 March; 32(3): 163-9 0098-1532

- **Long-term follow-up of the clinical efficacy of chemotherapy for acute myeloid leukemia at a single institute.**
  Author(s): First Department of Internal Medicine, Fukui Medical University, 23-3 Shimoaizuki, Matsuoka-cho, Yoshida, Fukui 910-1193, Japan.
  Source: Seo, T Fukushima, T Inoue, H Imamura, S Urasaki, Y Yoshida, A Kawai, Y Yamauchi, T Iwasaki, H Tsutani, H Nakamura, T Ueda, T J-Infect-Chemother. 2001 September; 7(3): 156-62 1341-321X

- **Lovastatin induces a pronounced differentiation response in acute myeloid leukemias.**
  Author(s): Department of Cellular and Molecular Biology, Ontario Cancer Institute, University Health Network, Toronto, Canada.
  Source: Dimitroulakos, J Thai, S Wasfy, G H Hedley, D W Minden, M D Penn, L Z Leuk-Lymphoma. 2000 December; 40(1-2): 167-78 1042-8194

- **Mitoxantrone, etoposide, and cyclosporine therapy in pediatric patients with recurrent or refractory acute myeloid leukemia.**
  Author(s): Division of Pediatric Oncology, Medical Oncology, and Clinical Pharmacology, Stanford University School of Medicine, Palo Alto, USA. Gary.Dahl@leland.stanford.edu
  Source: Dahl, G V Lacayo, N J Brophy, N Dunussi Joannopoulos, K Weinstein, H J Chang, M Sikic, B I Arceci, R J J-Clin-Oncol. 2000 May; 18(9): 1867-75 0732-183X

- **New clonal karyotypic abnormalities acquired following autologous bone marrow transplantation for acute myeloid leukemia do not appear to confer an adverse prognosis.**
  Author(s): The University of Toronto Autologous Blood and Marrow Transplant Program, The Toronto Hospital, The University of Toronto, Canada.
  Source: Imrie, K R Dube, I Prince, H M Girouard, C Crump, M Keating, A Bone-Marrow-Transplant. 1998 February; 21(4): 395-9 0268-3369

- **New developments in the treatment of acute myeloid leukemia: focus on topotecan.**
  Author(s): M.D. Anderson Cancer Center, Houston, TX 77030, USA.
  Source: Kantarjian, H Semin-Hematol. 1999 October; 36(4 Suppl 8): 16-25 0037-1963

- **Parallel phase I studies of daunorubicin given with cytarabine and etoposide with or without the multidrug resistance modulator PSC-833 in previously untreated patients 60 years of age or older with acute myeloid leukemia: results of cancer and leukemia group B study 9420.**
  Author(s): Greenebaum Cancer Center, University of Maryland School of Medicine, Baltimore, MD, USA.
  Source: Lee, E J George, S L Caligiuri, M Szatrowski, T P Powell, B L Lemke, S Dodge, R K Smith, R Baer, M Schiffer, C A J-Clin-Oncol. 1999 September; 17(9): 2831-9 0732-183X

- **Pharmacology of cytarabine given as a continuous infusion followed by mitoxantrone with and without amsacrine/etoposide as reinduction chemotherapy for relapsed or refractory pediatric acute myeloid leukemia.**
  Author(s): Department of Pediatrics, New York Medical College, Valhalla 10595, USA. mehmet-ozkaynak@nymc.edu
  Source: Ozkaynak, M F Avramis, V I Carcich, S Ortega, J A Med-Pediatr-Oncol. 1998 December; 31(6): 475-82 0098-1532

- **Reduced total number of cobblestone area forming cells and in vitro stromal-cell growth in autografts from acute myeloid leukemia patients.**
  Author(s): Department of Hematology, Aarhus University Hospital, Opgang 4A, DK 8000 Aarhus C, Denmark.
  Source: Olesen, G Tonder, H Hokland, P Cytotherapy. 2000; 2(3): 201-9 1465-3249

- **Tetraploidy in acute myeloid leukemia secondary to large cell lymphoma.**
  Author(s): University of Pittsburgh Medical Center, PA 15213, USA. kaplanss@msx.upmc.edu
  Source: Kaplan, S S Rybka, W B Blom, J Shekhter Levin, S Leuk-Lymphoma. 1998 November; 31(5-6): 617-23 1042-8194

- **The differentiating effect of retinoic acid and vincristine on acute myeloid leukemia.**
  Author(s): Department of Surgery, The Chinese University of Hong Kong, Sha Tin.
  Source: Leung, M F Wong, K F J-Hematother. 1999 June; 8(3): 275-9 1061-6128
- **The impact of karyotype on remission rates in adult patients with de novo acute myeloid leukemia receiving high-dose cytarabine-based induction chemotherapy.**
  Author(s): Leukaemia Unit, Royal Marsden Hospital, Surrey, UK. jmehta@exchange.uams.edu
  Source: Mehta, J Powles, R Treleaven, J Swansbury, G J Kulkarni, S Saso, R Min, T Singhal, S Leuk-Lymphoma. 1999 August; 34(5-6): 553-60 1042-8194
- **Total-body irradiation and melphalan is a safe and effective conditioning regimen for autologous bone marrow transplantation in children with acute myeloid leukemia in first remission. The Italian Association for Pediatric Hematology and Oncology-Bone Marrow Transplantation Group.**
  Author(s): Department of Pediatrics, University of Pavia, IRCCS Policlinico San Matteo, Pavia, Italy.
  Source: Bonetti, F Zecca, M Pession, A Messina, C Montagna, D Lanino, E Fagioli, F Santoro, N Prete, A Cesaro, S Rondelli, R Giorgiani, G De Stefano, P Locatelli, F J-Clin-Oncol. 1999 December; 17(12): 3729-35 0732-183X
- **Translocation (11;11)(p13- p15;q23) in a child with therapy-related acute myeloid leukemia following chemotherapy with DNA-topoisomerase II inhibitors for Langerhans cell histiocytosis.**
  Author(s): Laboratorio de Citogenetica, Centro de transplante de Medula Ossea (CEMO), Instituto Nacional de Cancer (INCA), Rio de Janeiro, Brazil. luizamacedo@hotmail.com
  Source: Silva, Maria Luiza Macedo Land, Marcelo Gerardin Poirot Maradei, Simone Otero, Luize Veith, Melissa Brito, Gilena Klumb, Claudete Fernandez, Teresa Pombo de Oliveira, Maria Socorro Cancer-Genet-Cytogenet. 2002 May; 135(1): 101-2 0165-4608
- **Use of peripheral blood stem cells for autologous transplantation in acute myeloid leukemia patients allows faster engraftment and equivalent disease-free survival compared with bone marrow cells.**
  Author(s): Institute of Haematology and Medical Oncology, 'Seragnoli', Bologna University, Bologna, Italy.
  Source: Visani, G Lemoli, R Tosi, P Martinelli, G Testoni, N Ricci, P Motta, M Gherlinzoni, F Leopardi, G Pastano, R Rizzi, S Piccaluga, P Isidori, A Tura, S Bone-Marrow-Transplant. 1999 September; 24(5): 467-72 0268-3369

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**

The following is a specific Web list relating to acute myeloid leukemia; 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:

- **Vitamins**

  Vitamin K
  Source: Healthnotes, Inc.; www.healthnotes.com

CHAPTER 3. ALTERNATIVE MEDICINE AND ACUTE MYELOID LEUKEMIA

Overview

In this chapter, we will begin by introducing you to official information sources on complementary and alternative medicine (CAM) relating to acute myeloid leukemia. 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 acute myeloid leukemia 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 "acute myeloid leukemia" (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 acute myeloid leukemia:

- **A feasibility study of simultaneous administration of gemtuzumab ozogamicin with intensive chemotherapy in induction and consolidation in younger patients with acute myeloid leukemia.**
  Author(s): Kell WJ, Burnett AK, Chopra R, Yin JA, Clark RE, Rohatiner A, Culligan D, Hunter A, Prentice AG, Milligan DW.
  Source: Blood. 2003 December 15; 102(13): 4277-83. Epub 2003 August 21.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12933575

- **A phase I study of induction chemotherapy for older patients with newly diagnosed acute myeloid leukemia (AML) using mitoxantrone, etoposide, and the MDR modulator PSC 833: a southwest oncology group study 9617.**
  Author(s): Chauncey TR, Rankin C, Anderson JE, Chen I, Kopecky KJ, Godwin JE, Kalaycio ME, Moore DF, Shurafa MS, Petersdorf SH, Kraut EH, Leith CP, Head DR, Luthardt FW, Willman CL, Appelbaum FR.

Source: Leukemia Research. 2000 July; 24(7): 567-74.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=10867130

- **A phase I/II study of intensive dose escalation of cytarabine in combination with idarubicin and etoposide in induction and consolidation treatment of adult acute myeloid leukemia. Australian Leukaemia Study Group (ALSG).**
Author(s): Lowenthal RM, Bradstock KF, Matthews JP, Bishop JF, Juneja S, Cobcroft R, Eliadis P, Enno A, Gill D, Herrmann RP, Manoharan A, Page FJ, Rooney KF, Rosenfeld D, Seldon M, Taylor KM, Wolf MM, Young GA.
Source: Leukemia & Lymphoma. 1999 August; 34(5-6): 501-10.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=10492073

- **A phase II study employing combination regimens containing KRN8602 in drug-resistant acute myeloid leukemia and acute lymphoblastic leukemia. KRN8602 Leukemia Study Group.**
Author(s): Kishimoto Y, Sampi K, Kuraishi Y, Takemoto Y, Okabe K, Tamura K, Mizoguchi H, Saito H, Masaoka T, Ogawa M.
Source: Anti-Cancer Drugs. 1999 March; 10(3): 267-73.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=10327031

- **A pilot study of busulfan, cyclophosphamide and etoposide followed by autologous transplantation for acute myeloid leukemia in remission.**
Author(s): Bilgrami S, Edwards RL, Bona RD, Kazierad D, Furlong F, Fox J, Clive J, Naqvi BH, Tutschka PJ.
Source: Acta Haematologica. 2000; 104(2-3): 144-7.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=11154994

- **A randomized study of high-dose cytarabine in induction in acute myeloid leukemia.**
Author(s): Bishop JF, Matthews JP, Young GA, Szer J, Gillett A, Joshua D, Bradstock K, Enno A, Wolf MM, Fox R, et al.
Source: Blood. 1996 March 1; 87(5): 1710-7.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=8634416

- **Acute myeloid leukemia and lung cancer occurring in a chronic lymphocytic leukemia patient treated with fludarabine and autologous peripheral blood stem-cell transplantation.**
Author(s): Meloni G, Proia A, Guerrisi V, Cordone I, De Cuia R, Fenu S, Mauro FR, Pescarmona E, Reato G, Mandelli F.
Source: Annals of Oncology : Official Journal of the European Society for Medical Oncology / Esmo. 2000 November; 11(11): 1493-5.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=11142491

- **Acute myeloid leukemia following therapy of Hodgkin's disease with radiotherapy and ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine).**
  Author(s): Lipton JH, Gospodarowicz M, Reingold S.
  Source: Hematological Oncology. 1996 March; 14(1): 29-31.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=8613133

- **Acute myeloid leukemia in patients treated for rhabdomyosarcoma with cyclophosphamide and low-dose etoposide on Intergroup Rhabdomyosarcoma Study III: an interim report.**
  Author(s): Heyn R, Khan F, Ensign LG, Donaldson SS, Ruymann F, Smith MA, Vietti T, Maurer HM.
  Source: Medical and Pediatric Oncology. 1994; 23(2): 99-106.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=8202048

- **Acute myeloid leukemia presenting as non-neutropenic colitis in an infant.**
  Author(s): Kohler H, Nurko S, Glickman J, Furuta GT.
  Source: Journal of Pediatric Gastroenterology and Nutrition. 2003 November; 37(5): 631-3.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14581811

- **Acute myeloid leukemia with t(11;19)(q23;p13) developing in an adult T-cell leukemia patient treated with combined chemotherapy including etoposide.**
  Author(s): Kanemura N, Tsurumi H, Hara T, Yamada T, Sawada M, Naito T, Moriwaki H.
  Source: International Journal of Hematology. 2001 December; 74(4): 475-6.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=11794709

- **An effective chemotherapeutic regimen for acute myeloid leukemia and myelodysplastic syndrome in children with Down's syndrome.**
  Author(s): Kojima S, Sako M, Kato K, Hosoi G, Sato T, Ohara A, Koike K, Okimoto Y, Nishimura S, Akiyama Y, Yoshikawa T, Ishii E, Okamura J, Yazaki M, Hayashi Y, Eguchi M, Tsukimoto I, Ueda K.
  Source: Leukemia : Official Journal of the Leukemia Society of America, Leukemia Research Fund, U.K. 2000 May; 14(5): 786-91.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=10803507

- **An evaluation of combinations of diaziquone, etoposide and mitoxantrone in the treatment of adults with relapsed or refractory acute myeloid leukemia: results of 8722, a randomized phase II study conducted by Cancer and Leukemia Group B.**
  Author(s): Lee EJ, George SL, Amrein PC, Paciucci PA, Allen SL, Schiffer CA.
  Source: Leukemia : Official Journal of the Leukemia Society of America, Leukemia Research Fund, U.K. 1998 February; 12(2): 139-43.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=9519774

- **Attempts to improve treatment outcomes in acute myeloid leukemia (AML) in older patients: the results of the United Kingdom Medical Research Council AML11 trial.**
  Author(s): Goldstone AH, Burnett AK, Wheatley K, Smith AG, Hutchinson RM, Clark RE; Medical Research Council Adult Leukemia Working Party.
  Source: Blood. 2001 September 1; 98(5): 1302-11.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=11520775

- **Autologous bone marrow transplantation for acute myeloid leukemia using 4-hydroperoxycyclophosphamide-purged bone marrow and the busulfan/etoposide preparative regimen: a follow-up report.**
  Author(s): Linker CA, Ries CA, Damon LE, Rugo HS, Wolf JL.
  Source: Bone Marrow Transplantation. 1998 November; 22(9): 865-72.
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  Author(s): Revesz D, Chelghoum Y, Le QH, Elhamri M, Michallet M, Thomas X.
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  Author(s): Gillis S, Dann EJ, Rund D.
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Author(s): Leung MF, Wong KF.
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  Author(s): Baines P, Fisher J, Truran L, Davies E, Hallett M, Hoy T, Burnett AK.
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  Author(s): Grimwade D, Walker H, Harrison G, Oliver F, Chatters S, Harrison CJ, Wheatley K, Burnett AK, Goldstone AH; Medical Research Council Adult Leukemia Working Party.
  Source: Blood. 2001 September 1; 98(5): 1312-20.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=11520776

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  Author(s): Visani G, Bernasconi P, Boni M, Castoldi GL, Ciolli S, Clavio M, Cox MC, Cuneo A, Del Poeta G, Dini D, Falzetti D, Fanin R, Gobbi M, Isidori A, Leoni F, Liso V, Malagola M, Martinelli G, Mecucci C, Piccaluga PP, Petti MC, Rondelli R, Russo D, Sessarego M, Specchia G, Testoni N, Torelli G, Mandelli F, Tura S.
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  Author(s): Wrzesien-Kus A, Robak T, Jamroziak K, Wierzbowska A, Dmoszynska A, Adamczyk-Cioch M, Kuliczkowski K, Mazur G, Holowiecki J, Konopka L, Maj S, Marianska B, Zawilska K; Polish Acute Leukemia Group (PALG) phase II study.
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  Author(s): Friedenberg WR, Miller HJ, Marx JJ Jr, Schloesser LL, Reding DJ, Mazza JJ, Hocking WG, Mercier RJ, Raich PC, Cassileth PA.
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Author(s): Milella M, Kornblau SM, Estrov Z, Carter BZ, Lapillonne H, Harris D, Konopleva M, Zhao S, Estey E, Andreeff M.
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http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=11560954

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Author(s): Steuber CP, Krischer J, Holbrook T, Camitta B, Land V, Sexauer C, Mahoney D, Weinstein H.
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Author(s): Bow EJ, Sutherland JA, Kilpatrick MG, Williams GJ, Clinch JJ, Shore TB, Rubinger M, Schacter BA.
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Author(s): Roulston D, Anastasi J, Rudinsky R, Nucifora G, Zeleznik-Le N, Rowley JD, McGavran L, Tsuchida M, Hayashi Y.
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- **Therapy-related acute myeloid leukemia following treatment with epipodophyllotoxins: estimating the risks.**
Author(s): Smith MA, Rubinstein L, Ungerleider RS.
Source: Medical and Pediatric Oncology. 1994; 23(2): 86-98. Review.
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- **Therapy-related acute myeloid leukemia with minimal myeloid differentiation (AML-M0) associated with a t(11;19)(q23;p13.3) translocation.**
Author(s): Suehiro Y, Uike N, Kumagawa M, Goto T, Muta K, Kozuru M.
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Author(s): Pedersen-Bjergaard J, Philip P, Larsen SO, Andersson M, Daugaard G, Ersboll J, Hansen SW, Hou-Jensen K, Nielsen D, Sigsgaard TC, et al.
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- **Time sequential chemotherapy for primary refractory or relapsed adult acute myeloid leukemia: results of the phase II Gemia protocol.**
Author(s): Martino R, Guardia R, Altes A, Sureda A, Brunet S, Sierra J.
Source: Haematologica. 1999 March; 84(3): 226-30.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=10189387

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Author(s): Archimbaud E, Leblond V, Fenaux P, Dombret H, Cordonnier C, Dreyfus F, Cony-Makhoul P, Tilly H, Troussard X, Auzanneau G, Thomas X, Ffrench M, Marie JP.
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Author(s): Archimbaud E, Thomas X, Leblond V, Michallet M, Fenaux P, Cordonnier C, Dreyfus F, Troussard X, Jaubert J, Travade P, et al.
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Author(s): Woods WG, Kobrinsky N, Buckley JD, Lee JW, Sanders J, Neudorf S, Gold S, Barnard DR, DeSwarte J, Dusenbery K, Kalousek D, Arthur DC, Lange BJ.
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Author(s): Vahrenwald F, Galka K, Jurgens G, Bruchelt G, Girgert R, Schweizer P.
Source: Leukemia Research. 1997 November-December; 21(11-12): 1071-6.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=9444941

- **Transfusion-related acute lung injury (TRALI) following allogeneic stem cell transplant for acute myeloid leukemia.**
Author(s): Ganguly S, Carrum G, Nizzi F, Heslop HE, Popat U.

Source: American Journal of Hematology. 2004 January; 75(1): 48-51.
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  Author(s): Silva ML, Land MG, Maradei S, Otero L, Veith M, Brito G, Klumb C, Fernandez T, Pombo-de-Oliveira MS.
  Source: Cancer Genetics and Cytogenetics. 2002 May; 135(1): 101-2.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12072208

- **Translocation (2;4)(p23;q25): an additional case of a new recurrent anomaly in acute myeloid leukemia.**
  Author(s): Shi G, Weh HJ, Hossfeld DK.
  Source: Cancer Genetics and Cytogenetics. 1993 October 15; 70(2): 140-1.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=8242596

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  Author(s): Loeb DM, Arceci RJ.
  Source: Blood. 2002 April 1; 99(7): 2626-7.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=11926186

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  Author(s): Sperr WR, Hauswirth AW, Wimazal F, Knobl P, Geissler K, Valent P.
  Source: Wiener Klinische Wochenschrift. 2003 August 14; 115(13-14): 505-14. Review.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=13677269

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  Author(s): Sandler ES, Friedman DJ, Mustafa MM, Winick NJ, Bowman WP, Buchanan GR.
  Source: Cancer. 1997 March 1; 79(5): 1049-54.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=9041170

- **Unrelated cord blood transplantation for childhood acute myeloid leukemia: a Eurocord Group analysis.**
  Author(s): Michel G, Rocha V, Chevret S, Arcese W, Chan KW, Filipovich A, Takahashi TA, Vowels M, Ortega J, Bordigoni P, Shaw PJ, Yaniv I, Machado A, Pimentel P, Fagioli F, Verdeguer A, Jouet JP, Diez B, Ferreira E, Pasquini R, Rosenthal J, Sievers E, Messina C, Iori AP, Garnier F, Ionescu I, Locatelli F, Gluckman E; Eurocord Group.
  Source: Blood. 2003 December 15; 102(13): 4290-7. Epub 2003 August 14. Review.
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- **Uptake and storage of retinol and retinyl esters in bone marrow of children with acute myeloid leukemia treated with high-dose retinyl palmitate.**
  Author(s): Skrede B, Lie SO, Blomhoff R, Norum KR.
  Source: European Journal of Haematology. 1994 March; 52(3): 140-4.
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- **Urinary excretion of proteolyzed alpha1-antitrypsin: specificity, quantitation, and relation to therapy response in patients with acute myeloid leukemia.**
  Author(s): Dengler R, Plewan A, Munstermann U, Busch R, Eger G, Emmerich B.
  Source: Clinical Cancer Research : an Official Journal of the American Association for Cancer Research. 1995 February; 1(2): 199-205.
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- **Use of peripheral blood stem cells for autologous transplantation in acute myeloid leukemia patients allows faster engraftment and equivalent disease-free survival compared with bone marrow cells.**
  Author(s): Visani G, Lemoli R, Tosi P, Martinelli G, Testoni N, Ricci P, Motta M, Gherlinzoni F, Leopardi G, Pastano R, Rizzi S, Piccaluga P, Isidori A, Tura S.
  Source: Bone Marrow Transplantation. 1999 September; 24(5): 467-72.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=10482929

- **Viridans streptococcal sepsis: clinical features and complications in childhood acute myeloid leukemia.**
  Author(s): Okamoto Y, Ribeiro RC, Srivastava DK, Shenep JL, Pui CH, Razzouk BI.
  Source: Journal of Pediatric Hematology/Oncology : Official Journal of the American Society of Pediatric Hematology/Oncology. 2003 September; 25(9): 696-703. Review.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12972804

- **Voriconazole in the management of invasive aspergillosis in two patients with acute myeloid leukemia undergoing stem cell transplantation.**
  Author(s): Mattei D, Mordini N, Lo Nigro C, Ghirardo D, Ferrua MT, Osenda M, Gallamini A, Bacigalupo A, Viscoli C.
  Source: Bone Marrow Transplantation. 2002 December; 30(12): 967-70.
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12476292

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/**

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 ACUTE MYELOID LEUKEMIA

Overview

In this chapter, we will give you a bibliography on recent dissertations relating to acute myeloid leukemia. 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 "acute myeloid leukemia" (or a synonym) in their titles. To accurately reflect the results that you might find while conducting research on acute myeloid leukemia, we have not necessarily excluded non-medical dissertations in this bibliography.

Dissertations on Acute Myeloid Leukemia

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 acute myeloid leukemia. 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:

- **Analysis of gene expression patterns in acute myeloid leukemia using microarray technology** by Orleth, Annette; PhD from Open University (United Kingdom), 2003
  http://wwwlib.umi.com/dissertations/fullcit/f503377
- **Clonality and cycling status of leukemic progenitors from patients with acute myeloid leukemia (AML)** by Guan, Yinghui; PhD from The University of British Columbia (Canada), 2003, 153 pages
  http://wwwlib.umi.com/dissertations/fullcit/NQ85450
- **Oncogene cooperation in the pathogenesis of acute myeloid leukemia** by Cuenco, Grace Montevirgen; PhD from Brandeis University, 2003, 213 pages
  http://wwwlib.umi.com/dissertations/fullcit/3081812

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 ACUTE MYELOID LEUKEMIA

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 "acute myeloid leukemia" (or a synonym) in their titles. To accurately reflect the results that you might find while conducting research on acute myeloid leukemia, we have not necessarily excluded non-medical patents in this bibliography.

Patents on Acute Myeloid Leukemia

By performing a patent search focusing on acute myeloid leukemia, 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 acute myeloid leukemia:

- **Amli-MTg8 fusion protein resulting from T(8;21) translocation in acute myeloid leukemia**

  Inventor(s): Kikuchi; Kimiko (Tokyo, JP), Kozu; Tomoko (Kitamoto, JP), Miyoshi; Hiroyuki (Ageo, JP), Ohki; Misao (Kokubunji, JP)

  Assignee(s): Srl, Inc. (tokyo, Jp)

  Patent Number: 5,580,727

  Date filed: August 15, 1994

  Abstract: Means for diagnosing t(8;21) translocation type **acute myeloid leukemia** with high sensitivity by a simple operation are disclosed. The present invention provided AML1-MTG8 fused DNA having the nucleotide sequence shown in SEQ ID No. 1 and DNA fragments thereof containing the fused site. The present invention provided AML1-MTG8 fused polypeptide having the amino acid sequence shown in SEQ ID No. 2, and fragments thereof containing the fused site. The present invention provided AML1-MTG8 fused mRNA having the same nucleotide sequence as shown in SEQ ID No. 1 except that thymine is replaced with uracil, and fragments thereof. The present invention provided a probe which is said DNA fragment that is labelled. The present invention provided a method for detecting said fused DNA by using said probe. The present invention provided a method for detecting AML1-MTG8 fused mRNA or a fragment thereof in a sample, comprising the steps of amplifying said fused DNA or a fragment thereof by a nucleic acid-amplifying method and detecting the amplified DNA fragment.

  Excerpt(s): The present invention relates to novel DNAs, polypeptides encoded thereby and methods for detecting the DNAs and the polypeptides. The present invention is useful for diagnosis of t(8;21) translocation type **acute myeloid leukemia.** The t(8;21) translocation type **acute myeloid leukemia** is an **acute myeloid leukemia** (hereinafter also referred to as "AML") which accompanies translocation of a gene on chromosome 8 to chromosome 21, which is one the most frequent acute myeloid leukemias ranking with t(15;17) translocation type **acute myeloid leukemia.** The t(8;21)(q22;q22) translocation type **acute myeloid leukemia** morphologically associates with FAB-M2 subtype of AML (Fourth International Workshop on Chromosomes in Leukemia, 1982, Cancer Genet. Cytogenet. 11, 284 (1984); J. D. Rowley, Sem. Hematol. 27, 122 (1990)). Leukemic cells with the t(8;21) translocation are uniquely characterized by a high frequency of Auer rods and mutation of granulocytic line (R. Berger et al., Blood 59, 171 (1982)). Cytogenetically, this translocation is often accompanied by a loss of sex chromosome which is rarely observed in acute leukemias without t(8;21) translocation. Diagnosis of t(8;21) translocation type AML can be attained by detecting the above-mentioned features or by analyzing the chromosomes. However, these methods are troublesome and the sensitivity of the diagnosis is not satisfactory.

  Web site: http://www.delphion.com/details?pn=US05580727__

- **Method for treating T-lineage leukemias and lymphomas using a CD7-specific monoclonal antibody (TXU-7) linked to the pokeweed antiviral protein (PAP)**

  Inventor(s): Uckun; Fatih M. (White Bear Lake, MN)

  Assignee(s): Regents of the University of Minnesota (minneapolis, Mn)

  Patent Number: 6,689,362

  Date filed: December 3, 1999

  Abstract: Acute lymphoblastic leukemia (ALL) and **acute myeloid leukemia** (AML) are common leukemias in both children and adults. Current treatment strategies are inadequate and often result in patient toxicity and relapse. Accordingly, the need exists for a T-cell-specific immunotoxin with sufficient stability and efficacy to eliminate cell populations associated with various T-cell malignancies. The present invention addresses this concern by providing a biotherapeutic agent (e.g., an immunoconjugate or immunotoxin) comprising a monoclonal antibody (MoAb TXU-7) specific to mammalian T-cell/myeloid antigen CD7 linked to the pokeweed antiviral protein (PAP). The CD7 antigen is expressed on human T-lineage lymphoid cells and leukemic progenitor cells in T-lineage lymphoid malignancies. PAP is a member of the hemitoxin group of toxins and inactivates ribosomes by the removal of a single adenosine from the conserved loop sequence found near the 3' terminus of all larger RNAs. This specific depurination abrogates the ability of elongation factors to interact with ribosomes and results in irreversible shut-down of protein synthesis. The PAP toxin was linked to the TXU-7 Mab to produce a TXU-7-PAP immunoconjugate. This immunotoxin is stable in vivo and effective in killing and eliminating CD7-expressing T-lineage leukemic cells.

  Excerpt(s): Acute lymphoblastic leukemia (ALL) is the most common form of childhood malignancy. Champlin et al., Blood, 73, 2051 (1989). Each year about 1250 children less than 15 years of age are found to have acute lymphoblastic leukemia. Champlin et al., cited supra. Recently, dramatic improvements in the multiagent chemotherapy of children with ALL have resulted in cure rates of 70-75%. Poplack et al., Pediatric Clinics of North America, 35, 903 (1988). However, despite these recent improvements, as many as 1 in 5 patients will eventually suffer leukemic relapse. Riehm et al., Haematol. Blood Transf., 33, 439 (1990). This occurrence of relapsed patients equates to 250 cases/year and is equivalent to the number of newly diagnosed cases of childhood acute nonlymphoblastic leukemia, medulloblastoma, and rhabxomyosarcoma Furthermore, this relapse rate surpasses the number of newly diagnosed cases of childhood Ewings sarcoma, osteogenic sarcoma, hepatoma, and germ cell tumors. The unsatisfactory outcome of this population makes a significant contribution to overall pediatric cancer mortality, despite the excellent outcome for the substantial majority of children with ALL. Currently, the major challenge in the treatment of childhood ALL is to cure patients who have relapsed despite intensive multiagent chemotherapy. Champlin et al., cited supra. For patients who have relapsed while on therapy or shortly after elective cessation of therapy, the overall survival is very poor. Poplack et al., cited supra. Treatment of these relapsed children has generally employed either intensive chemotherapy to achieve a second remission, subsequent use of either nonablative chemotherapy or ablative radiochemotherapy and bone marrow transplantation (BMT). Kersey et al., N Engl. J. Med., 117, 461 (1987). However, recurrence of leukemia is the major obstacle to the success of either approach. Dicke et al., Clin. Hematol., 15, 86 (1986). Furthermore, treatment of these relapsed patients by the intensification of cytotoxic therapy using conventional drugs-will likely cause overlapping toxicities and may result in delays which may erode the intensity of therapy. Consequently, the development of new potent anti-ALL drugs and the design of combinative treatment

protocols utilizing these new agents, have emerged as focal points for research in the therapy of relapsed ALL.

Web site: http://www.delphion.com/details?pn=US06689362__

- **Transcription factor, BP1**

  Inventor(s): Berg; Patricia E. (Accokeek, MD)

  Assignee(s): George Washington University (washington, Dc)

  Patent Number: 6,416,956

  Date filed: August 11, 2000

  Abstract: An isolated DNA of SEQ ID NO: 1 is provided that encodes the transcription factor BP1, which is believed to be a repressor of the.beta.-globin gene. A host cell that is transformed with a vector that contains the DNA may be used to produce BP1. Vectors having a controllable promoter operably connected to the BP1 open reading frame may be used to transform.beta.-globin producing cells of patients with sickle cell anemia, thereby providing a treatment. Because BP1 is overexpressed in leukemia and breast cancer cells, **acute myeloid leukemia,** acute lymphocytic leukemia, and breast cancer can be screened for and diagnosed by determining whether BP1 is overexpressed in cell samples of patients who may have these conditions. An antisense DNA or RNA to the DNA encoding BP1 may be used as a treatment for **acute myeloid leukemia,** acute lymphocytic leukemia, and breast cancer.

  Excerpt(s): The present invention relates to a DNA that encodes the transcription factor BP1, a vector containing the DNA and a host cell containing the DNA. The invention also relates to an antisense DNA or RNA to the DNA encoding BP1, methods for treating sickle cell anemia by administering an effective amount of BP1, and methods for screening for **acute myeloid leukemia,** acute lymphocytic leukemia, and breast cancer. Expression of globin genes in the.beta.-globin cluster is restricted to erythropoietic cells, with five different genes expressed during embryonic (.epsilon.), fetal (G.gamma. and A.gamma.) and adult (.delta. and.beta.) development. Transcriptional activation of globin genes occurs not only by binding of transcriptional activator proteins to the promoter of the gene being activated, but also by a regulatory element located 6-18 kb upstream of the.beta.-globin cluster, the Locus Control Region (LCR) (See, for example, Berg, P. E. and A. N. Schechter. 1992. Molecular genetics of disorders of hemoglobin. In T. Friedmann (ed), Molecular Genetic Medicine. Academic Press, San Diego.; Forrester, W. C., C. Thompson, J. T. Elder, and Groudine, M. 1986. A developmentally stable chromatin structure in the human.beta.-globin gene cluster. Proc. Natl. Acad. Sci. USA 83: 1359-1363.; and Tuan, D., W. Soloman, Q. Li, and I. M. London. 1985. The ".beta.-like-globin" gene domain in human erythroid cells. Proc. Natl. Acad. Sci. USA 82: 6384-6388.). Sequential activation of the.beta.-globin cluster genes during ontogeny must be countered by repression of the globin genes inactive during a given developmental stage. Repression is caused by binding of repressor proteins to promoter/upstream DNA and, in the case of the adult.beta.-globin gene, is probably also due to lack of activation by the LCR (see, for example, Crossley, M. and S. H. Orkin. 1993. Regulation of the.beta.-globin locus. Curr. Opinion Gen. Dev. 3: 232-237.). While much is known about transcriptional activators that bind to DNA sequences near the.beta.-globin gene, little is known about the proteins that repress its transcription. As discussed below, BP1 is shown to bind to two silencer DNA sequences upstream of the.beta.-globin gene and therefore, there is strong evidence suggesting that BP1 protein is a repressor of the.beta.-globin gene. The present invention provides for a DNA sequence that encodes BP1, and

methods of using information derived from knowledge of the DNA sequence to screen for conditions such as breast cancer, **acute myeloid leukemia** and acute lymphocytic leukemia. The DNA sequence was found to be closely related to two other human genes, DLX4 and DLX7, described in Quinn, L. M., B. V. Johnson, J. Nicholl, G. R. Sutherland, and B. Kalionis. 1997. Isolation and identification of homeobox genes from human placenta including a novel member of the Distal-less family, DLX4. Gene 187: 55-61 and Nakamura S, Stock DW, Wydner KL, Bollekens JA, Takeshita K, Nagai BM, Chiba , Kitamura T, Freeland TM, Zhao Z, Minowada J, Lawrence JB, Weiss KB, and Ruddle FH. Genomic analysis of a new mammalian Distal-less gene: D1x-7. Genomics 1996; 38: 314-324.

Web site: http://www.delphion.com/details?pn=US06416956__

Patent Applications on Acute Myeloid Leukemia

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 acute myeloid leukemia:

- **Classification and prognosis prediction of acute lymphoblastic leukemia by gene expression profiling**

  Inventor(s): Downing, James R.; (Cordova, TN), Wilkins, Dawn E.; (Oxford, MS), Wong, Limsoon; (Singapore, SG), Yeoh, Eng-Juh; (Singapore, SG)

  Correspondence: Alston And Bird Llp; ST. Jude Children's Research Hospital; Bank OF America Plaza; 101 South Tryon Street, Suite 4000; Charlotte; NC; 28280-4000; US

  Patent Application Number: 20040018513

  Date filed: March 18, 2003

  Abstract: The present invention provides methods and compositions useful for diagnosing and choosing treatment for leukemia patients. The claimed methods include methods of assigning a subject affected by leukemia to a leukemia risk group, methods of predicting whether a subject affected by leukemia has an increased risk of relapse, methods of predicting whether a subject affected by leukemia has an increased risk of developing secondary **acute myeloid leukemia,** methods to aid in the determination of a prognosis for a subject affected by leukemia, methods of choosing a therapy for a subject affected by leukemia, and methods of monitoring the disease state in a subject undergoing one or more therapies for leukemia. The claimed compositions include arrays having capture probes for the differentially-expressed genes of the invention, computer readable media having digitally-encoded expression profiles associated with leukemia risk groups, and kits for diagnosing and choosing therapy for leukemia patients.

  Excerpt(s): This application claims the benefit of U.S. Provisional Application No. 60/367,144 filed Mar. 22, 2002, which is hereby incorporated in its entirety by reference herein. Pediatric acute lymphoblastic leukemia (ALL) is one of the great success stories of modern cancer therapy, with contemporary treatment protocols achieving overall long-term event free survival rates approaching 80% (Schrappe et al. (2000) Blood

[9] This has been a common practice outside the United States prior to December 2000.

95:3310-22; Silverman et al.(2001) Blood 97:1211-18; and Pui and Evans (1998) N. Eng. J. Med. 339:605-15). This success has been achieved in part by using risk-adapted therapy that involves tailoring the intensity of treatment to each patient's risk of relapse. This approach was developed following the realization that pediatric ALL is a heterogeneous disease consisting of various leukemia subtypes that differ markedly in their response to chemotherapy (reviewed in Pui and Evans (1998) N. Eng. J. Med. 339:605-15). By tailoring the intensity of treatment to a patient's relative risk of relapse, patients are neither under-treated or over-treated, and are thus afforded the highest chance for a cure. Unfortunately, the accurate assignment of patients to specific risk groups is a difficult and expensive process, requiring intensive laboratory studies including immunophenotyping, cytogenetics, and molecular diagnostics (Pui and Evans (1998) N. Eng. J. Med. 339:605-15; and Pui et al. (2001) Lancet Oncology 2:597-607). Moreover, these diagnostic approaches require the collective expertise of a number of professionals, and although this expertise is available at most major medical centers, it is generally unavailable in developing countries. Accordingly, there remains a need for rapid, less expensive methods of assigning patients affected by ALL into known leukemia risk groups and identifying patients for whom there is a high risk that conventional therapeutic approaches will fail.

Web site: http://appft1.uspto.gov/netahtml/PTO/search-bool.html

- **Evi27 gene sequences and protein encoded thereby**

  Inventor(s): Shaughnessy, John D.; (Little Rock, AR)

  Correspondence: Benjamin Aaron Adler; Adler & Associates; 8011 Candle Lane; Houston; TX; 77071; US

  Patent Application Number: 20020102639

  Date filed: February 2, 2001

  Abstract: The present invention describes the cloning and molecular and cellular characterization of a novel protein with homology to the IL-17 receptor. The gene was cloned by virtue of its proximity to a common site of retroviral integration in a murine **acute myeloid leukemia.** The gene described herein possibly codes for a novel interleukin receptor that binds an as yet unidentified cytokine ligand, and may be useful in cancer diagnostics and therapies that rely on immune system modulation.

  Excerpt(s): This non-provisional patent application claims benefit of provisional patent application U.S. Ser. No. 60/180,374, filed Feb. 4, 2000, now abandoned. The present invention relates generally to the field of molecular biology. More specifically, the present invention relates to the cloning and characterization of a murine and human gene that encodes a novel protein with homology to the IL-17 receptor. Retroviral insertional mutagenesis in BXH2 and AKXD recombinant inbred (RI) mice induces a high incidence of myeloid leukemia and the proviral integration sites in the leukemias provide powerful genetic tags for disease gene identification (Bedigian et al., 1984; Gilbert et al., 1993). During the past several years, a number of disease genes have been identified in these leukemias by proviral tagging. These disease genes include a tumor suppressor gene, neurofibromatosis type 1 (Nf1); a gene with homology to the lymphoid-restricted type II membrane protein Jaw1, Mrv integration site 1 (Mrvi1); a gene encoding a hematopoietic cell growth and differentiation factor, myeloblastosis oncogene (Myb); three homeobox genes, homeobox A7 (Hoxa7), homeobox A9 (Hoxa9), and myeloid ecotropic viral integration site 1 (Meis1); a zinc-finger protein (Evi1); and a gene with homology to the ubiquitin-specific protease 8 (Usp8) oncogene and to genes

encoding various cell cycle regulatory proteins, ecotropic viral integration site 5 (Evi5) (Buchberg et al., 1990, Viskochil et al., 1990, Shaughnessy et al., 1999; Copeland and Jenkins, 1999, Nakamura et al., 1996a, Morishita et al., 1988, Liao, et al., 1997). Four of the genes are proven or suspected human disease genes: EVI1, NF1 and HOXA9 are causally associated with myeloid leukemia and EVI5 with stage 4S neuroblastoma (Ogawa et al., 1996, Copeland and Jenkins, 1999, Nakamura et al., 1996b, Roberts et al. 1998), validating the usefulness of this approach for human disease gene identification.

Web site: http://appft1.uspto.gov/netahtml/PTO/search-bool.html

- **Methods for the diagnosis and prognosis of acute leukemias**

  Inventor(s): Anderson, Gary E.; (Kingston, CA), Dunne, Roderick J.; (Kingston, CA), Lepage, Marc A.; (Kingston, CA), Misener, Stephen R.; (Perth, CA), Steeg, Evan W.; (Kingston, CA), Willis, Edward S.; (Nepean, CA)

  Correspondence: Sterne, Kessler, Goldstein & Fox P.L.L.C.; Attorneys AT Law; Suite 600; 1100 New York Avenue, N.W.; Washington; DC; 20005-3934; US

  Patent Application Number: 20010044103

  Date filed: December 1, 2000

  Abstract: The present invention relates to the diagnosis of the distinction between acute lymphoblastic leukemia (ALL) and **acute myeloid leukemia** (AML) and prognosis of AML. Disclosed is a means to diagnose the distinction between ALL and AML employing measurement of the abundance of the nucleic acid or protein products of small combinations (two, three or more) of particular human genes. The invention further describes the use of the measurement of the abundance of the nucleic acid or protein product of two human genes for prognostic indication in AML. The invention also relates to therapies targeted at these indicator genes, and the screening of drugs for cancer that target these indicator genes or their protein products.

  Excerpt(s): The present application claims priority benefit of U.S. Application Ser. No. 60/168,625, filed Dec. 3, 1999, the entire disclosure of which is incorporated by reference herein. The present invention relates to methods of classifying acute leukemias. More particularly, the invention relates to methods of distinguishing **acute myeloid leukemia** (AML) from acute lymphoblastic leukemia (ALL) by measuring the nucleic acid levels or gene product (protein) levels of small combinations (two, three or more) of particular human genes. The invention is also useful as a prognostic indicator in AML. A major challenge of cancer treatment has been to target specific therapies to pathogenically distinct tumor types, to maximize efficacy and minimize toxicity. Improvements in cancer classification have thus been central to advances in cancer treatment.

  Web site: http://appft1.uspto.gov/netahtml/PTO/search-bool.html

- **Methods of therapy and diagnosis using targeting of cells that express toll-like receptor proteins**

  Inventor(s): Dedea, Douglas; (Castro Valley, CA)

  Correspondence: Luisa Bigornia; Hyseq, INC.; 670 Almanor Avenue; Sunnyvale; CA; 94085; US

  Patent Application Number: 20040022786

  Date filed: November 22, 2002

  Abstract: Certain cells, including types of cancer cells such as B-cell lymphomas, T cell lymphomas, Hodgkin's disease and myeloid leukemias, are capable of expressing Toll-like Receptor 9 (TLR9) or Toll-like Receptor 10 (TLR10) mRNA. Immunotargeting using TLR9 or TLR10 polypeptides, nucleic acids encoding for TLR9 or TLR10 polypeptides and anti-TLR9 or anti-TLR10 antibodies provides a method of killing or inhibiting that growth of cancer cells that express the TLR9 or TLR10 protein. Methods of immunotherapy and diagnosis of disorders associated with TLR9 or TLR10 protein-expressing cells, such as B-cell lymphoma, T cell lymphoma, **acute myeloid leukemia,** Hodgkin's disease, B cell leukemia, chronic lymphocytic leukemia, chronic myelogenous leukemia and myelodysplastic syndromes, are described.

  Excerpt(s): This application is a continuation-in-part of U.S. application Ser. No. 10/077,676 filed on Feb. 14, 2002, entitled "Methods of Therapy and Diagnosis Using Targeting of Cells that Expressing Toll-Like Receptor 9 Protein", Attorney Docket No. HYS-49, which in turn is a continuation-in-part of U.S. application Ser. No. 09/687,527 filed on Oct. 12, 2000, entitled "Full Length Novel Nucleic Acids and Polypeptides", Attorney Docket No. 795, and U.S. application Ser. No. 09/488,725 filed on Jan. 21, 2000, entitled "Novel Contigs Obtained from Various Libraries," Attorney Docket No. 784. This and all other U.S. Patents and Patent Applications cited herein are hereby incorporated by reference in their entirety. This invention relates to compositions and methods for targeting Toll-like Receptor 9 (TLR9) protein- and Toll-like Receptor 10 (TLR10) protein-expressing cells and their use in the therapy and diagnosis of various pathological states, including cancer, autoimmune disease, organ transplant rejection, and allergic reactions. Antibody therapy for cancer involves the use of antibodies, or antibody fragments, against a tumor antigen to target antigen-expressing cells. Antibodies, or antibody fragments, may have direct or indirect cytotoxic effects or may be conjugated or fused to cytotoxic moieties. Direct effects include the induction of apoptosis, the blocking of growth factor receptors, and anti-idiotype antibody formation. Indirect effects include antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-mediated cellular cytotoxicity (CMCC). When conjugated or fused to cytotoxic moieties, the antibodies, or fragments thereof, provide a method of targeting the cytotoxicity towards the tumor antigen expressing cells. (Green, et al., Cancer Treatment Reviews, 26:269-286 (2000)).

  Web site: http://appft1.uspto.gov/netahtml/PTO/search-bool.html

- **Novel transcription factor, BP1**

  Inventor(s): Berg, Patricia E.; (Accokeek, MD)

  Correspondence: Antonelli, Terry, Stout & Kraus, Llp; 1300 North Seventeenth Street; Suite 1800; Arlington; VA; 22209-9889; US

  Patent Application Number: 20030171273

  Date filed: May 14, 2002

  Abstract: An isolated DNA of SEQ ID NO:1 is provided that encodes the transcription factor BP1, which is believed to be a repressor of the.beta.-globin gene. A host cell that is transformed with a vector that contains the DNA may be used to produce BP1. Vectors having a controllable promoter operably connected to the BPl open reading frame may be used to transform.beta.-globin producing cells of patients with sickle cell anemia, thereby providing a treatment. Because BP1 is overexpressed in leukemia and breast cancer cells, **acute myeloid leukemia,** acute lymphocytic leukemia, and breast cancer can be screened for and diagnosed by determining whether BP1 is overexpressed in cell samples of patients who may have these conditions. An antisense DNA or RNA to the DNA encoding BP1 may be used as a treatment for **acute myeloid leukemia,** acute lymphocytic leukemia, and breast cancer.

  Excerpt(s): The present application claims the benefit of the filing date of U.S. Provisional Application No. 60/148,940, filed Aug. 13, 1999. The provisional application is incorporated by reference herein. Work described herein was supported by NIH grant R01DK53533. The U.S. Government has certain rights in the invention. The present invention relates to a DNA that encodes the transcription factor BP1, a vector containing the DNA and a host cell containing the DNA. The invention also relates to an antisense DNA or RNA to the DNA encoding BP1, methods for treating sickle cell anemia by administering an effective amount of BP1, and methods for screening for **acute myeloid leukemia,** acute lymphocytic leukemia, and breast cancer.

  Web site: http://appft1.uspto.gov/netahtml/PTO/search-bool.html

- **Specific human antibodies for selective cancer therapy**

  Inventor(s): Guy, Rachel; (Rehovot, IL), Hagay, Yocheved; (Rehovot, IL), Lazarovits, Janette; (Reut, IL), Levanon, Avigdor; (Rehovot, IL), Lifshitz, Orly; (Rishon Lezion, IL), Peretz, Tuvia; (Hod Hasharon, IL), Plaksin, Daniel; (Rehovot, IL), Szanton, Esther; (Rehovot, IL)

  Correspondence: Kenyon & Kenyon; One Broadway; New York; NY; 10004; US

  Patent Application Number: 20040073011

  Date filed: December 31, 2001

  Abstract: The present invention is directed to a peptide or polypeptide comprising an Fv molecule, a construct thereof, a fragment of either, or a construct of a fragment having enhanced binding characteristics so as to bind selectively and/or specifically to a target cell in favor of other cells, wherein the binding selectivity or specificity is primarily determined by a first hypervariable region, and wherein the Fv is a scFv or a dsFv, and optionally having one or more tags. The enhanced binding is directed to a substantially exposed and/or over-expressed binding site on or in a target comprising a cell in favor of other cells on or in which the binding site is not substantially available and/or expressed. The invention is further directed to a method for isolating such peptides and

polypeptides from a phage display library and to the nucleic acid molecules encoding them. The invention provides for a pharmaceutical composition comprising the peptide or polypeptide and kits for diagnosis and treatment of disease, specifically cancer, most specifically **acute myeloid leukemia.**

Excerpt(s): This application claims priority to provisional application Serial No. 60/258,948, filed on Dec. 29, 2000, the subject matter of which is incorporated by reference hereto. The present invention relates to the field of tissue targeting and identification, with the aid of phage display technology, of peptides and polypeptides that specifically bind to target cells. Such peptides and polypeptides are Fv molecules, constructs thereof, fragments of either or constructs of a fragment. More particularly, the peptides and polypeptides may have anti-cancer activity, and/or are associated with, or conjugated to, anti-cancer agents, especially against blood-related cancers. Tissue-selective targeting of therapeutic agents is an emerging discipline in the pharmaceutical industry. New cancer treatments based on targeting have been designed to increase the specificity and potency of the treatment, while reducing toxicity, thereby enhancing overall efficacy. Mouse monoclonal antibodies (MAb's) to tumor-associated antigens have been employed in an attempt to target toxin, radionucleotide, and chemotherapeutic conjugates to tumors. In addition, differentiation antigens, such as CD 19, CD20, CD22 and CD25, have been exploited as cancer specific targets in treating hematopoietic malignancies. Although extensively studied, this approach has several limitations. One limitation is the difficulty of isolating appropriate monoclonal antibodies that display selective binding. A second limitation is the need for high antibody immunogenicity as a prerequisite for successful antibody isolation. A third limitation is the elicitation in the patient of an immune response against murine antibodies (human anti-mouse antibody-HAMA response) that often results in a shorter serum half-life, and prevents repetitive treatments, thus diminishing the therapeutic value of the antibody. This latter limitation has stimulated interest both in engineering chimeric or humanized monoclonal antibodies of murine origin, and in discovering human antibodies.

Web site: http://appft1.uspto.gov/netahtml/PTO/search-bool.html

- **Therapeutic methods for acute myeloid leukemia**

  Inventor(s): Lee, Robert J.; (Columbus, OH), Ratnam, Manohar; (Toledo, OH)

  Correspondence: Calfee Halter & Griswold, Llp; 800 Superior Avenue; Suite 1400; Cleveland; OH; 44114; US

  Patent Application Number: 20030170299

  Date filed: February 27, 2003

  Abstract: The invention provides a method for treating leukemia in a patient. The method comprises administering to the patient a substance that increases expression of folate receptor.beta. on leukemia cells in the patient, called a FR-.beta. inducer, and administering a folate-conjugated therapeutic that targets the leukemia cells in the patient. The invention also comprises pharmaceutical compositions containing one or both of a FR-.beta. inducer and a folate-conjugated therapeutic. The invention also provides a kit for use in treating leukemia in a patient, the kit comprising an FR-.beta. inducer and a folate-conjugated therapeutic

  Excerpt(s): This application claims priority from U.S. Provisional Patent Application Serial No. 60/360,408, filed on Feb. 27, 2002, which is incorporated herein by reference.

This invention was made, at least in part, with government support under National Institutes of Health R01 Grants CA80183 and CA70873. The U.S. government has certain rights in the invention. This invention relates to methods for treating leukemia. More specifically, this invention relates to methods for treating patients with myeloid leukemia, preferably acute myelogenous leukemia (AML), by administering agents that increase levels of folate receptor.beta. (FR-.beta.), and then treating the patient with folate-conjugated anticancer therapeutic agents. Leukemias are neoplastic disorders involving cells of the blood-forming organs. Leukemias are commonly classified as either myeloid or lymphoid. Myeloid leukemias involve the myeloid elements of the bone marrow--white cells, red cells and megakaryocytes. Myeloid leukemia, which accounts for half of all leukemia cases, is classified as acute myelogenous leukemia (AML) or chronic myelogenous leukemia (CML). AML is the most common form of leukemia in adults and is classified according to the French-American-British (FAB) criteria into classes M0-M7 based on the degree of differentiation and the extent of cell maturation. Standard AML chemotherapy, which often includes an anthracycline, results in a 70% complete remission (CR) rate in AML patients. Anthracycline therapy, however, is associated with severe side effects, including myelosuppression and dose-limiting cardiotoxicity, as well as a significant incidence of relapse. Less than 20% of CR patients survive in the long term.

Web site: http://appft1.uspto.gov/netahtml/PTO/search-bool.html

- **Treatment of acute myeloid leukemia with indolinone compounds**

  Inventor(s): Cherrington, Julie; (San Francisco, CA), O'Farrell, Anne-Marie; (Menlo Park, CA)

  Correspondence: Foley And Lardner; Suite 500; 3000 K Street NW; Washington; DC; 20007; US

  Patent Application Number: 20030130280

  Date filed: October 28, 2002

  Abstract: A method of treating **acute myeloid leukemia** in patient positive for FLT-3-ITD is described. The treatment is accomplished by administration of a compound of Formula I or II as defined herein.

  Excerpt(s): This application claims priority to U.S. Provisional Patent Application Serial No. 60/330,623, which is hereby incorporated in its entirety by reference. The invention relates to a method of treating **acute myeloid leukemia** by administering an indolinone compound. **Acute myeloid leukemia** (AML) is a disease in which cancerous cells develop in the blood and bone marrow. Untreated AML is a fatal disease with median survival time of 3 months. Patients with AML that are FLT-3-ITD (internal tandem duplication) positive typically exhibit poor response to traditional chemotherapy. The present invention is directed to treating AML patients and preferably patients positive for FLT-3-ITD but not restricted to FLT-3-ITD by administering indolinone compounds of Formula I or II. The present invention also is directed to a method of inhibiting phosphorylation of FLT-3. Acute myeloid leukemia, also called acute non-lymphocytic leukemia, is a form of cancer in which too many immature white blood cells are found in the blood and bone marrow. These immature cells, also called blasts, have failed to develop into mature infection-fighting cells.

  Web site: http://appft1.uspto.gov/netahtml/PTO/search-bool.html

- **Tumor-associated antigen RHAMM**

  Inventor(s): Greiner, Jochen; (Ulm, DE), Schmitt, Michael; (Ulm, DE)

  Correspondence: Wolf Greenfield & Sacks, PC; Federal Reserve Plaza; 600 Atlantic Avenue; Boston; MA; 02210-2211; US

  Patent Application Number: 20030170755

  Date filed: September 26, 2002

  Abstract: The invention provides methods for diagnosing cancer including **acute myeloid leukemia** and chronic myeloid leukemia, based on the identification of certain cancer-associated polypeptides as antigens that elicit immune responses in cancer. The identified antigens can be utilized as markers for diagnosing cancer, and for following the course of treatment of cancer.

  Excerpt(s): This application claims priority under 35 U.S.C.sctn.119 from U.S. provisional application serial No. 60/324,989, filed Sep. 26, 2001. The invention relates to use of novel tumor-associated antigens in the diagnosis of cancer, including acute and chronic myeloid leukemia. The myeloid leukemias are members of a heterogeneous group of diseases characterized by infiltration of the blood, bone marrow, and other tissues by neoplastic cells of the hematopoietic system. There is a spectrum of symptoms of the mycloid leukemias, which range from to slowly progressive to rapidly fatal. (see; Harrison's Principles of Internal Medicine, 14/e, McGraw-Hill Companies, New York, 1998). Myeloid leukemias are categorized as either **acute myeloid leukemia** (AML) or chronic myeloid leukemia (CML) and they differ in their progression and prognosis. The onset of AML may be genetically based, or the result of exposure to radiation, chemicals, or drugs such as antineoplastic drugs used in cancer treatment. CML is also linked to chromosomal abnormalities and its progression is influenced by exposure to radiation and/or chemicals.

  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 acute myeloid leukemia, 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 "acute myeloid leukemia" (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 acute myeloid leukemia.

You can also use this procedure to view pending patent applications concerning acute myeloid leukemia. 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. PERIODICALS AND NEWS ON ACUTE MYELOID LEUKEMIA

Overview

In this chapter, we suggest a number of news sources and present various periodicals that cover acute myeloid leukemia.

News Services and Press Releases

One of the simplest ways of tracking press releases on acute myeloid leukemia 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 "acute myeloid leukemia" (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 acute myeloid leukemia. 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 "acute myeloid leukemia" (or synonyms). The following was recently listed in this archive for acute myeloid leukemia:

- **Early blast clearance predicts better outcome in acute myeloid leukemia**
  Source: Reuters Medical News
  Date: February 10, 2003

- **Outcomes poor and costs high in elderly with acute myeloid leukemia**
  Source: Reuters Medical News
  Date: August 05, 2002
- **Tyrosine kinase inhibitor kills acute myeloid leukemia cells with receptor mutation**
  Source: Reuters Industry Breifing
  Date: July 31, 2001
- **Autologous bone marrow transplant of little benefit for acute myeloid leukemia in remission**
  Source: Reuters Medical News
  Date: January 10, 2001
- **IL-12-expressing acute myeloid leukemia cells might eliminate residual disease**
  Source: Reuters Medical News
  Date: December 23, 1999
- **Cosmic radiation may increase risk of acute myeloid leukemia in jet pilots**
  Source: Reuters Medical News
  Date: December 10, 1999
- **Autologous Bone Marrow Transplant Lowers Risk Of Acute Myeloid Leukemia Relapse**
  Source: Reuters Medical News
  Date: March 09, 1998
- **Threshold For Platelet Transfusion In Acute Myeloid Leukemia Can Be Lowered**
  Source: Reuters Medical News
  Date: December 25, 1997
- **Macrophage Colony-Stimulating Factor Effective Therapy For Acute Myeloid Leukemia Patients**
  Source: Reuters Medical News
  Date: August 28, 1997
- **Acyclovir Effective Prophylaxis Against Oral Ulcers In Patients With Acute Myeloid Leukemia**
  Source: Reuters Medical News
  Date: May 16, 1995

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 "acute myeloid leukemia" (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 "acute myeloid leukemia" (or synonyms). If you know the name of a company that is relevant to acute myeloid leukemia, 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 "acute myeloid leukemia" (or synonyms).

Academic Periodicals covering Acute Myeloid Leukemia

Numerous periodicals are currently indexed within the National Library of Medicine's PubMed database that are known to publish articles relating to acute myeloid leukemia. In addition to these sources, you can search for articles covering acute myeloid leukemia 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 7. 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 acute myeloid leukemia. 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).

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.

Researching Orphan Drugs

Although the list of orphan drugs is revised on a daily basis, you can quickly research orphan drugs that might be applicable to acute myeloid leukemia by using the database managed by the National Organization for Rare Disorders, Inc. (NORD), at **http://www.rarediseases.org/**. Scroll down the page, and on the left toolbar, click on "Orphan Drug Designation Database." On this page (**http://www.rarediseases.org/search/noddsearch.html**), type "acute myeloid leukemia" (or synonyms) into the search box, and click "Submit Query." When you receive your results, note that not all of the drugs may be relevant, as some may have been withdrawn from orphan status. Write down or print out the name of each drug and the relevant contact information. From there, visit the Pharmacopeia Web site and type the name of each orphan drug into the search box at **http://www.nlm.nih.gov/medlineplus/druginformation.html**. You may need to contact the sponsor or NORD for further information.

NORD conducts "early access programs for investigational new drugs (IND) under the Food and Drug Administration's (FDA's) approval 'Treatment INDs' programs which allow for a limited number of individuals to receive investigational drugs before FDA marketing approval." If the orphan product about which you are seeking information is approved for

marketing, information on side effects can be found on the product's label. If the product is not approved, you may need to contact the sponsor.

The following is a list of orphan drugs currently listed in the NORD Orphan Drug Designation Database for acute myeloid leukemia:

- **Gemtuzumab Zogamicin**
  http://www.rarediseases.org/nord/search/nodd_full?code=1004
- **Histamine (trade name: Maxamine)**
  http://www.rarediseases.org/nord/search/nodd_full?code=1009
- **Mitoxantrone HCL (trade name: Novantrone)**
  http://www.rarediseases.org/nord/search/nodd_full?code=115
- **2-chlorodeoxyadenosine**
  http://www.rarediseases.org/nord/search/nodd_full?code=2
- **Idarubicin HC1 for injection (trade name: Idamycin)**
  http://www.rarediseases.org/nord/search/nodd_full?code=775
- **Filgrastim (trade name: Neupogen)**
  http://www.rarediseases.org/nord/search/nodd_full?code=800
- **Cladribine (trade name: Laustatin)**
  http://www.rarediseases.org/nord/search/nodd_full?code=881

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 "acute myeloid leukemia" (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	21453
Books / Periodicals / Audio Visual	71
Consumer Health	1135
Meeting Abstracts	21
Other Collections	197
Total	22877

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 "acute myeloid leukemia" (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 acute myeloid leukemia 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 acute myeloid leukemia. 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 acute myeloid leukemia. 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 "acute myeloid leukemia":

Bone Marrow Diseases
http://www.nlm.nih.gov/medlineplus/bonemarrowdiseases.html

Bone Marrow Transplantation
http://www.nlm.nih.gov/medlineplus/bonemarrowtransplantation.html

Lymphoma
http://www.nlm.nih.gov/medlineplus/lymphoma.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 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 acute myeloid leukemia. 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 acute myeloid leukemia. By consulting all of associations listed in this chapter, you will have nearly exhausted all sources for patient associations concerned with acute myeloid leukemia.

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 acute myeloid leukemia. 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 "acute myeloid leukemia" (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 "acute myeloid leukemia". 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 "acute myeloid leukemia" (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 "acute myeloid leukemia" (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**

ACUTE MYELOID LEUKEMIA DICTIONARY

The definitions below are derived from official public sources, including the National Institutes of Health [NIH] and the European Union [EU].

6-Mercaptopurine: An antimetabolite antineoplastic agent with immunosuppressant properties. It interferes with nucleic acid synthesis by inhibiting purine metabolism and is used, usually in combination with other drugs, in the treatment of or in remission maintenance programs for leukemia. [NIH]

Aberrant: Wandering or deviating from the usual or normal course. [EU]

Acatalasia: A rare autosomal recessive disorder resulting from the absence of catalase activity. Though usually asymptomatic, a syndrome of oral ulcerations and gangrene may be present. [NIH]

Accommodation: Adjustment, especially that of the eye for various distances. [EU]

Acetylcholine: A neurotransmitter. Acetylcholine in vertebrates is the major transmitter at neuromuscular junctions, autonomic ganglia, parasympathetic effector junctions, a subset of sympathetic effector junctions, and at many sites in the central nervous system. It is generally not used as an administered drug because it is broken down very rapidly by cholinesterases, but it is useful in some ophthalmological applications. [NIH]

Acetyltransferases: Enzymes catalyzing the transfer of an acetyl group, usually from acetyl coenzyme A, to another compound. EC 2.3.1. [NIH]

Aclarubicin: An anthracycline antibiotic produced by Streptomyces galilaeus. It has potent antineoplastic activity, especially in the treatment of leukemias, with reduced cardiac toxicity in comparison to daunorubicin or doxorubicin. [NIH]

Acoustic: Having to do with sound or hearing. [NIH]

Actin: Essential component of the cell skeleton. [NIH]

Acute Disease: Disease having a short and relatively severe course. [NIH]

Acute leukemia: A rapidly progressing cancer of the blood-forming tissue (bone marrow). [NIH]

Acute lymphoblastic leukemia: ALL. A quickly progressing disease in which too many immature white blood cells called lymphoblasts are found in the blood and bone marrow. Also called acute lymphocytic leukemia. [NIH]

Acute lymphocytic leukemia: ALL. A quickly progressing disease in which too many immature white blood cells called lymphoblasts are found in the blood and bone marrow. Also called acute lymphoblastic leukemia. [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]

Adaptability: Ability to develop some form of tolerance to conditions extremely different from those under which a living organism evolved. [NIH]

Adenine: A purine base and a fundamental unit of adenine nucleotides. [NIH]

Adenosine: A nucleoside that is composed of adenine and d-ribose. Adenosine or adenosine derivatives play many important biological roles in addition to being components of DNA and RNA. Adenosine itself is a neurotransmitter. [NIH]

Adjuvant: A substance which aids another, such as an auxiliary remedy; in immunology, nonspecific stimulator (e.g., BCG vaccine) of the immune response. [EU]

Adjuvant Therapy: Treatment given after the primary treatment to increase the chances of a cure. Adjuvant therapy may include chemotherapy, radiation therapy, or hormone therapy. [NIH]

Adoptive Transfer: Form of passive immunization where previously sensitized immunologic agents (cells or serum) are transferred to non-immune recipients. When transfer of cells is used as a therapy for the treatment of neoplasms, it is called adoptive immunotherapy (immunotherapy, adoptive). [NIH]

Adrenal Cortex: The outer layer of the adrenal gland. It secretes mineralocorticoids, androgens, and glucocorticoids. [NIH]

Adverse Effect: An unwanted side effect of treatment. [NIH]

Aerosol: A solution of a drug which can be atomized into a fine mist for inhalation therapy. [EU]

Aetiology: Study of the causes of disease. [EU]

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]

Agar: A complex sulfated polymer of galactose units, extracted from Gelidium cartilagineum, Gracilaria confervoides, and related red algae. It is used as a gel in the preparation of solid culture media for microorganisms, as a bulk laxative, in making emulsions, and as a supporting medium for immunodiffusion and immunoelectrophoresis. [NIH]

Algorithms: A procedure consisting of a sequence of algebraic formulas and/or logical steps to calculate or determine a given task. [NIH]

Alkaline: Having the reactions of an alkali. [EU]

Alkylating Agents: Highly reactive chemicals that introduce alkyl radicals into biologically active molecules and thereby prevent their proper functioning. Many are used as antineoplastic agents, but most are very toxic, with carcinogenic, mutagenic, teratogenic, and immunosuppressant actions. They have also been used as components in poison gases. [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]

Allogeneic: Taken from different individuals of the same species. [NIH]

Allogeneic bone marrow transplantation: A procedure in which a person receives stem cells, the cells from which all blood cells develop, from a compatible, though not genetically identical, donor. [NIH]

Allografts: A graft of tissue obtained from the body of another animal of the same species but with genotype differing from that of the recipient; tissue graft from a donor of one genotype to a host of another genotype with host and donor being members of the same species. [NIH]

Alopecia: Absence of hair from areas where it is normally present. [NIH]

Alpha Particles: Positively charged particles composed of two protons and two neutrons, i.e., helium nuclei, emitted during disintegration of very heavy isotopes; a beam of alpha particles or an alpha ray has very strong ionizing power, but weak penetrability. [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]

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 Acids: Organic compounds that generally contain an amino (-NH2) and a carboxyl (-COOH) group. Twenty alpha-amino acids are the subunits which are polymerized to form proteins. [NIH]

Amino Acids: Organic compounds that generally contain an amino (-NH2) and a carboxyl (-COOH) group. Twenty alpha-amino acids are the subunits which are polymerized to form proteins. [NIH]

Amino-terminal: The end of a protein or polypeptide chain that contains a free amino group (-NH2). [NIH]

Amplification: The production of additional copies of a chromosomal DNA sequence, found as either intrachromosomal or extrachromosomal DNA. [NIH]

Amsacrine: N-(4-(9-Acridinylamino)-3-methoxyphenyl)methanesulfonamide. Aminoacridine derivative that is a potent intercalating antineoplastic agent. It is effective in the treatment of acute leukemias and malignant lymphomas, but has poor activity in the treatment of solid tumors. It is frequently used in combination with other antineoplastic agents in chemotherapy protocols. It produces consistent but acceptable myelosuppression and cardiotoxic effects. [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]

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]

Analytes: A component of a test sample the presence of which has to be demonstrated. The term "analyte" includes where appropriate formed from the analyte during the analyses. [NIH]

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]

Anaplasia: Loss of structural differentiation and useful function of neoplastic cells. [NIH]

Anaplastic: A term used to describe cancer cells that divide rapidly and bear little or no resemblance to normal cells. [NIH]

Anemia: A reduction in the number of circulating erythrocytes or in the quantity of hemoglobin. [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]

Annealing: The spontaneous alignment of two single DNA strands to form a double helix. [NIH]

Antagonism: Interference with, or inhibition of, the growth of a living organism by another living organism, due either to creation of unfavorable conditions (e. g. exhaustion of food supplies) or to production of a specific antibiotic substance (e. g. penicillin). [NIH]

Antecedent: Existing or occurring before in time or order often with consequential effects. [EU]

Anthracycline: A member of a family of anticancer drugs that are also antibiotics. [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]

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]

Antibody therapy: Treatment with an antibody, a substance that can directly kill specific tumor cells or stimulate the immune system to kill tumor cells. [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-infective: An agent that so acts. [EU]

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]

Antineoplastic: Inhibiting or preventing the development of neoplasms, checking the maturation and proliferation of malignant cells. [EU]

Antineoplastic Agents: Substances that inhibit or prevent the proliferation of neoplasms. [NIH]

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]

Antiviral: Destroying viruses or suppressing their replication. [EU]

Anus: The opening of the rectum to the outside of the body. [NIH]

Aplasia: Lack of development of an organ or tissue, or of the cellular products from an organ or tissue. [EU]

Aplastic anemia: A condition in which the bone marrow is unable to produce blood cells. [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]

Applicability: A list of the commodities to which the candidate method can be applied as presented or with minor modifications. [NIH]

Aqueous: Having to do with water. [NIH]

Arginine: An essential amino acid that is physiologically active in the L-form. [NIH]

Arsenic trioxide: An anticancer drug that induces programmed cell death (apoptosis) in certain cancer cells. [NIH]

Arterial: Pertaining to an artery or to the arteries. [EU]

Artery: Vessel-carrying blood from the heart to various parts of the body. [NIH]

Ascorbic Acid: A six carbon compound related to glucose. It is found naturally in citrus fruits and many vegetables. Ascorbic acid is an essential nutrient in human diets, and necessary to maintain connective tissue and bone. Its biologically active form, vitamin C, functions as a reducing agent and coenzyme in several metabolic pathways. Vitamin C is considered an antioxidant. [NIH]

Aspergillosis: Infections with fungi of the genus Aspergillus. [NIH]

Aspirate: Fluid withdrawn from a lump, often a cyst, or a nipple. [NIH]

Assay: Determination of the amount of a particular constituent of a mixture, or of the

biological or pharmacological potency of a drug. [EU]

Atmospheric Pressure: The pressure at any point in an atmosphere due solely to the weight of the atmospheric gases above the point concerned. [NIH]

Attenuated: Strain with weakened or reduced virulence. [NIH]

Authorship: The profession of writing. Also the identity of the writer as the creator of a literary production. [NIH]

Autoimmune disease: A condition in which the body recognizes its own tissues as foreign and directs an immune response against them. [NIH]

Autologous: Taken from an individual's own tissues, cells, or DNA. [NIH]

Autologous bone marrow transplantation: A procedure in which bone marrow is removed from a person, stored, and then given back to the person after intensive treatment. [NIH]

Azacitidine: A pyrimidine analogue that inhibits DNA methyltransferase, impairing DNA methylation. It is also an antimetabolite of cytidine, incorporated primarily into RNA. Azacytidine has been used as an antineoplastic agent. [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]

Base: In chemistry, the nonacid part of a salt; a substance that combines with acids to form salts; a substance that dissociates to give hydroxide ions in aqueous solutions; a substance whose molecule or ion can combine with a proton (hydrogen ion); a substance capable of donating a pair of electrons (to an acid) for the formation of a coordinate covalent bond. [EU]

Basement Membrane: Ubiquitous supportive tissue adjacent to epithelium and around smooth and striated muscle cells. This tissue contains intrinsic macromolecular components such as collagen, laminin, and sulfated proteoglycans. As seen by light microscopy one of its subdivisions is the basal (basement) lamina. [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]

Beta 2-Microglobulin: An 11 kDa protein associated with the outer membrane of many cells including lymphocytes. It is the small subunit of the MHC class I molecule. Association with beta 2-microglobulin is generally required for the transport of class I heavy chains from the endoplasmic reticulum to the cell surface. Beta 2-microglobulin is present in small amounts in serum, csf, and urine of normal people, and to a much greater degree in the urine and plasma of patients with tubular proteinemia, renal failure, or kidney transplants. [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]

Bilirubin: A bile pigment that is a degradation product of heme. [NIH]

Binding Sites: The reactive parts of a macromolecule that directly participate in its specific combination with another molecule. [NIH]

Biochemical: Relating to biochemistry; characterized by, produced by, or involving chemical reactions in living organisms. [EU]

Biological response modifier: BRM. A substance that stimulates the body's response to

infection and disease. [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]

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]

Biomolecular: A scientific field at the interface between advanced computing and biotechnology. [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]

Biotin: Hexahydro-2-oxo-1H-thieno(3,4-d)imidazole-4-pentanoic acid. Growth factor present in minute amounts in every living cell. It occurs mainly bound to proteins or polypeptides and is abundant in liver, kidney, pancreas, yeast, and milk.The biotin content of cancerous tissue is higher than that of normal tissue. [NIH]

Bispecific antibodies: Antibodies developed in the laboratory to recognize more than one protein on the surface of different cells. Examples include bispecific antibodies 2B1, 520C9xH22, mDX-H210, and MDX447. [NIH]

Blastocyst: The mammalian embryo in the post-morula stage in which a fluid-filled cavity, enclosed primarily by trophoblast, contains an inner cell mass which becomes the embryonic disc. [NIH]

Blasts: Immature blood cells. [NIH]

Bleomycin: A complex of related glycopeptide antibiotics from Streptomyces verticillus consisting of bleomycin A2 and B2. It inhibits DNA metabolism and is used as an antineoplastic, especially for solid tumors. [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 vessel: A tube in the body through which blood circulates. Blood vessels include a network of arteries, arterioles, capillaries, venules, and veins. [NIH]

Blood-Brain Barrier: Specialized non-fenestrated tightly-joined endothelial cells (tight junctions) that form a transport barrier for certain substances between the cerebral capillaries and the brain tissue. [NIH]

Blot: To transfer DNA, RNA, or proteins to an immobilizing matrix such as nitrocellulose. [NIH]

Blotting, Western: Identification of proteins or peptides that have been electrophoretically separated by blotting and transferred to strips of nitrocellulose paper. The blots are then detected by radiolabeled antibody probes. [NIH]

Body Fluids: Liquid components of living organisms. [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]

Bone Marrow Cells: Cells contained in the bone marrow including fat cells, stromal cells, megakaryocytes, and the immediate precursors of most blood cells. [NIH]

Bone Marrow Transplantation: The transference of bone marrow from one human or animal to another. [NIH]

Brachytherapy: A collective term for interstitial, intracavity, and surface radiotherapy. It uses small sealed or partly-sealed sources that may be placed on or near the body surface or within a natural body cavity or implanted directly into the tissues. [NIH]

Bradykinin: A nonapeptide messenger that is enzymatically produced from kallidin in the blood where it is a potent but short-lived agent of arteriolar dilation and increased capillary permeability. Bradykinin is also released from mast cells during asthma attacks, from gut walls as a gastrointestinal vasodilator, from damaged tissues as a pain signal, and may be a neurotransmitter. [NIH]

Broad-spectrum: Effective against a wide range of microorganisms; said of an antibiotic. [EU]

Bronchi: The larger air passages of the lungs arising from the terminal bifurcation of the trachea. [NIH]

Bronchial: Pertaining to one or more bronchi. [EU]

Bryostatin-1: A drug used for its antitumor activity. [NIH]

Buccal: Pertaining to or directed toward the cheek. In dental anatomy, used to refer to the buccal surface of a tooth. [EU]

Busulfan: An anticancer drug that belongs to the family of drugs called alkylating agents. [NIH]

Bypass: A surgical procedure in which the doctor creates a new pathway for the flow of body fluids. [NIH]

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]

Callus: A callosity or hard, thick skin; the bone-like reparative substance that is formed round the edges and fragments of broken bone. [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]

Carbon Dioxide: A colorless, odorless gas that can be formed by the body and is necessary for the respiration cycle of plants and animals. [NIH]

Carboplatin: An organoplatinum compound that possesses antineoplastic activity. [NIH]

Carboxy: Cannabinoid. [NIH]

Carcinogen: Any substance that causes cancer. [NIH]

Carcinogenesis: The process by which normal cells are transformed into cancer cells. [NIH]

Carcinogenic: Producing carcinoma. [EU]

Cardiac: Having to do with the heart. [NIH]

Cardiotoxic: Having a poisonous or deleterious effect upon the heart. [EU]

Cardiotoxicity: Toxicity that affects the heart. [NIH]

Cardiovascular: Having to do with the heart and blood vessels. [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]

Castor Oil: Oil obtained from seeds of Ricinus communis that is used as a cathartic and as a plasticizer. [NIH]

Catalase: An oxidoreductase that catalyzes the conversion of hydrogen peroxide to water and oxygen. It is present in many animal cells. A deficiency of this enzyme results in acatalasia. EC 1.11.1.6. [NIH]

Catalytic Domain: The region of an enzyme that interacts with its substrate to cause the enzymatic reaction. [NIH]

Catheters: A small, flexible tube that may be inserted into various parts of the body to inject or remove liquids. [NIH]

Causal: Pertaining to a cause; directed against a cause. [EU]

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 Adhesion: Adherence of cells to surfaces or to other 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 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 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]

Cell Transplantation: Transference of cells within an individual, between individuals of the same species, or between individuals of different species. [NIH]

Central Nervous System: The main information-processing organs of the nervous system, consisting of the brain, spinal cord, and meninges. [NIH]

Centrioles: Self-replicating, short, fibrous, rod-shaped organelles. Each centriole is a short cylinder containing nine pairs of peripheral microtubules, arranged so as to form the wall of the cylinder. [NIH]

Centrosome: The cell center, consisting of a pair of centrioles surrounded by a cloud of amorphous material called the pericentriolar region. During interphase, the centrosome nucleates microtubule outgrowth. The centrosome duplicates and, during mitosis, separates to form the two poles of the mitotic spindle (mitotic spindle apparatus). [NIH]

Ceramide: A type of fat produced in the body. It may cause some types of cells to die, and is being studied in cancer treatment. [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]

Chemopreventive: Natural or synthetic compound used to intervene in the early precancerous stages of carcinogenesis. [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]

Chemotherapeutic agent: A drug used to treat cancer. [NIH]

Chemotherapeutics: Noun plural but singular or plural in constructions : chemotherapy. [EU]

Chemotherapy: Treatment with anticancer drugs. [NIH]

Chimeras: Organism that contains a mixture of genetically different cells. [NIH]

Chimeric Proteins: Proteins in individuals that are derived from genetically 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]

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]

Chondrocytes: Polymorphic cells that form cartilage. [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]

Chromosome Abnormalities: Defects in the structure or number of chromosomes resulting in structural aberrations or manifesting as disease. [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 granulocytic leukemia: A slowly progressing disease in which too many white blood cells are made in the bone marrow. Also called chronic myelogenous leukemia or chronic myeloid leukemia. [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 renal: Slow and progressive loss of kidney function over several years, often resulting in end-stage renal disease. People with end-stage renal disease need dialysis or transplantation to replace the work of the kidneys. [NIH]

Ciliary: Inflammation or infection of the glands of the margins of the eyelids. [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]

Cladribine: An antineoplastic agent used in the treatment of lymphoproliferative diseases including hairy-cell leukemia. [NIH]

Clear cell carcinoma: A rare type of tumor of the female genital tract in which the inside of the cells looks clear when viewed under a microscope. [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]

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]

Coenzyme: An organic nonprotein molecule, frequently a phosphorylated derivative of a water-soluble vitamin, that binds with the protein molecule (apoenzyme) to form the active enzyme (holoenzyme). [EU]

Cofactor: A substance, microorganism or environmental factor that activates or enhances the action of another entity such as a disease-causing agent. [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]

Colitis: Inflammation of the colon. [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]

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]

Colony-Stimulating Factors: Glycoproteins found in a subfraction of normal mammalian plasma and urine. They stimulate the proliferation of bone marrow cells in agar cultures and the formation of colonies of granulocytes and/or macrophages. The factors include interleukin-3 (IL-3), granulocyte colony-stimulating factor (G-CSF), macrophage colony-stimulating factor (M-CSF), and granulocyte-macrophage colony-stimulating factor (GM-CSF). [NIH]

Combination chemotherapy: Treatment using more than one anticancer drug. [NIH]

Communis: Common tendon of the rectus group of muscles that surrounds the optic foramen and a portion of the superior orbital fissure, to the anterior margin of which it is attached at the spina recti lateralis. [NIH]

Compassionate: A process for providing experimental drugs to very sick patients who have no treatment options. [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]

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]

Complete remission: The disappearance of all signs of cancer. Also called a complete response. [NIH]

Complete response: The disappearance of all signs of cancer in response to treatment. This does not always mean the cancer has been cured. [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]

Concomitant: Accompanying; accessory; joined with another. [EU]

Confounding: Extraneous variables resulting in outcome effects that obscure or exaggerate the "true" effect of an intervention. [NIH]

Conjugated: Acting or operating as if joined; simultaneous. [EU]

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]

Consolidation: The healing process of a bone fracture. [NIH]

Consolidation therapy: Chemotherapy treatments given after induction chemotherapy to further reduce the number of cancer cells. [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]

Continuous infusion: The administration of a fluid into a blood vessel, usually over a prolonged period of time. [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]

Controlled study: An experiment or clinical trial that includes a comparison (control) group. [NIH]

Corpus: The body of the uterus. [NIH]

Corpus Luteum: The yellow glandular mass formed in the ovary by an ovarian follicle that has ruptured and discharged its ovum. [NIH]

Cortisone: A natural steroid hormone produced in the adrenal gland. It can also be made in the laboratory. Cortisone reduces swelling and can suppress immune responses. [NIH]

Cranial: Pertaining to the cranium, or to the anterior (in animals) or superior (in humans) end of the body. [EU]

Crossing-over: The exchange of corresponding segments between chromatids of homologous chromosomes during meiosia, forming a chiasma. [NIH]

CSF: Cerebrospinal fluid. The fluid flowing around the brain and spinal cord. CSF is produced in the ventricles of the brain. [NIH]

Cues: Signals for an action; that specific portion of a perceptual field or pattern of stimuli to which a subject has learned to respond. [NIH]

Culture Media: Any liquid or solid preparation made specifically for the growth, storage, or transport of microorganisms or other types of cells. The variety of media that exist allow for the culturing of specific microorganisms and cell types, such as differential media, selective media, test media, and defined media. Solid media consist of liquid media that have been solidified with an agent such as agar or gelatin. [NIH]

Curative: Tending to overcome disease and promote recovery. [EU]

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]

Cyclin: Molecule that regulates the cell cycle. [NIH]

Cyclophosphamide: Precursor of an alkylating nitrogen mustard antineoplastic and immunosuppressive agent that must be activated in the liver to form the active aldophosphamide. It is used in the treatment of lymphomas, leukemias, etc. Its side effect, alopecia, has been made use of in defleecing sheep. Cyclophosphamide may also cause sterility, birth defects, mutations, and cancer. [NIH]

Cyclosporine: A drug used to help reduce the risk of rejection of organ and bone marrow transplants by the body. It is also used in clinical trials to make cancer cells more sensitive to anticancer drugs. [NIH]

Cyst: A sac or capsule filled with fluid. [NIH]

Cytarabine: An anticancer drug that belongs to the family of drugs called antimetabolites. [NIH]

Cytidine: A pyrimidine nucleoside that is composed of the base cytosine linked to the five-carbon sugar D-ribose. [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]

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]

Cytosine: A pyrimidine base that is a fundamental unit of nucleic acids. [NIH]

Cytoskeleton: The network of filaments, tubules, and interconnecting filamentous bridges which give shape, structure, and organization to the cytoplasm. [NIH]

Cytotoxic: Cell-killing. [NIH]

Cytotoxicity: Quality of being capable of producing a specific toxic action upon cells of special organs. [NIH]

Dacarbazine: An anticancer drug that belongs to the family of drugs called alkylating agents. [NIH]

Daunorubicin: Very toxic anthracycline aminoglycoside antibiotic isolated from Streptomyces peucetius and others, used in treatment of leukemias and other neoplasms. [NIH]

De novo: In cancer, the first occurrence of cancer in the body. [NIH]

Decidua: The epithelial lining of the endometrium that is formed before the fertilized ovum reaches the uterus. The fertilized ovum embeds in the decidua. If the ovum is not fertilized, the decidua is shed during menstruation. [NIH]

Decitabine: An anticancer drug that belongs to the family of drugs called antimetabolites. [NIH]

Deletion: A genetic rearrangement through loss of segments of DNA (chromosomes), bringing sequences, which are normally separated, into close proximity. [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]

Deoxyribonucleotides: A purine or pyrimidine base bonded to a deoxyribose containing a bond to a phosphate group. [NIH]

Depolarization: The process or act of neutralizing polarity. In neurophysiology, the reversal of the resting potential in excitable cell membranes when stimulated, i.e., the tendency of the cell membrane potential to become positive with respect to the potential outside the cell. [EU]

Depsipeptide: Anticancer drugs obtained from microorganisms. [NIH]

DES: Diethylstilbestrol. A synthetic hormone that was prescribed from the early 1940s until 1971 to help women with complications of pregnancy. DES has been linked to an increased risk of clear cell carcinoma of the vagina in daughters of women who used DES. DES may also increase the risk of breast cancer in women who used DES. [NIH]

Deuterium: Deuterium. The stable isotope of hydrogen. It has one neutron and one proton in the nucleus. [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]

Dexamethasone: (11 beta,16 alpha)-9-Fluoro-11,17,21-trihydroxy-16-methylpregna-1,4-diene-3,20-dione. An anti-inflammatory glucocorticoid used either in the free alcohol or esterified form in treatment of conditions that respond generally to cortisone. [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]

Diaziquone: AZQ. An anticancer drug that is able to cross the blood-brain barrier and kill cancer cells in the central nervous system. [NIH]

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]

Dihydrotestosterone: Anabolic agent. [NIH]

Diphtheria: A localized infection of mucous membranes or skin caused by toxigenic strains of Corynebacterium diphtheriae. It is characterized by the presence of a pseudomembrane at the site of infection. Diphtheria toxin, produced by C. diphtheriae, can cause myocarditis, polyneuritis, and other systemic toxic effects. [NIH]

Diphtheria Toxin: A 60 kD single chain protein elaborated by Corynebacterium diphtheriae that causes the sign and symptoms of diphtheria; it can be broken into two unequal fragments, the smaller (A fragment) inhibits protein synthesis and is the lethal moiety that needs the larger (B fragment) for entry into cells. [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]

Discriminant Analysis: A statistical analytic technique used with discrete dependent variables, concerned with separating sets of observed values and allocating new values. It is sometimes used instead of regression analysis. [NIH]

Disease Progression: The worsening of a disease over time. This concept is most often used for chronic and incurable diseases where the stage of the disease is an important determinant of therapy and prognosis. [NIH]

Disease-Free Survival: Period after successful treatment in which there is no appearance of the symptoms or effects of the disease. [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]

Diuresis: Increased excretion of urine. [EU]

Dose-limiting: Describes side effects of a drug or other treatment that are serious enough to prevent an increase in dose or level of that treatment. [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]

Doxorubicin: Antineoplastic antibiotic obtained from Streptomyces peucetics. It is a hydroxy derivative of daunorubicin and is used in treatment of both leukemia and solid tumors. [NIH]

Drive: A state of internal activity of an organism that is a necessary condition before a given stimulus will elicit a class of responses; e.g., a certain level of hunger (drive) must be present before food will elicit an eating response. [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]

Dura mater: The outermost, toughest, and most fibrous of the three membranes (meninges) covering the brain and spinal cord; called also pachymeninx. [EU]

Dysplasia: Cells that look abnormal under a microscope but are not cancer. [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]

Effector cell: A cell that performs a specific function in response to a stimulus; usually used to describe cells in the immune system. [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]

Elective: Subject to the choice or decision of the patient or physician; applied to procedures that are advantageous to the patient but not urgent. [EU]

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]

Embryo: The prenatal stage of mammalian development characterized by rapid morphological changes and the differentiation of basic structures. [NIH]

Embryogenesis: The process of embryo or embryoid formation, whether by sexual (zygotic) or asexual means. In asexual embryogenesis embryoids arise directly from the explant or on

intermediary callus tissue. In some cases they arise from individual cells (somatic cell embryoge). [NIH]

Encapsulated: Confined to a specific, localized area and surrounded by a thin layer of tissue. [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]

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]

Endothelium-derived: Small molecule that diffuses to the adjacent muscle layer and relaxes it. [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]

End-stage renal: Total chronic kidney failure. When the kidneys fail, the body retains fluid and harmful wastes build up. A person with ESRD needs treatment to replace the work of the failed kidneys. [NIH]

Enhancer: 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 Induction: An increase in the rate of synthesis of an enzyme due to the presence of an inducer which acts to derepress the gene responsible for enzyme synthesis. [NIH]

Enzyme Repression: The interference in synthesis of an enzyme due to the elevated level of an effector substance, usually a metabolite, whose presence would cause depression of the gene responsible for enzyme synthesis. [NIH]

Eosinophil: A polymorphonuclear leucocyte with large eosinophilic granules in its cytoplasm, which plays a role in hypersensitivity reactions. [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]

Epidemiological: Relating to, or involving epidemiology. [EU]

Epidermal: Pertaining to or resembling epidermis. Called also epidermic or epidermoid. [EU]

Epidermal Growth Factor: A 6 kD polypeptide growth factor initially discovered in mouse submaxillary glands. Human epidermal growth factor was originally isolated from urine based on its ability to inhibit gastric secretion and called urogastrone. epidermal growth factor exerts a wide variety of biological effects including the promotion of proliferation and differentiation of mesenchymal and epithelial cells. [NIH]

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]

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]

Erythema: Redness of the skin produced by congestion of the capillaries. This condition may result from a variety of causes. [NIH]

Erythema Infectiosum: Contagious infection with human B19 Parvovirus most commonly seen in school age children and characterized by fever, headache, and rashes of the face, trunk, and extremities. It is often confused with rubella. [NIH]

Erythrocytes: Red blood cells. Mature erythrocytes are non-nucleated, biconcave disks containing hemoglobin whose function is to transport oxygen. [NIH]

Erythroid Progenitor Cells: Committed, erythroid stem cells derived from myeloid stem cells. The progenitor cells develop in two phases: erythroid burst-forming units (BFU-E) followed by erythroid colony-forming units (CFU-E). BFU-E differentiate into CFU-E on stimulation by erythropoietin, and then further differentiate into erythroblasts when stimulated by other factors. [NIH]

Erythroleukemia: Cancer of the blood-forming tissues in which large numbers of immature, abnormal red blood cells are found in the blood and bone marrow. [NIH]

Escalation: Progressive use of more harmful drugs. [NIH]

Estrogen: One of the two female sex hormones. [NIH]

Estrogen receptor: ER. Protein found on some cancer cells to which estrogen will attach. [NIH]

Ethylnitrosourea: A nitrosourea compound with alkylating, carcinogenic, and mutagenic properties. [NIH]

Etoposide: A semisynthetic derivative of podophyllotoxin that exhibits antitumor activity. Etoposide inhibits DNA synthesis by forming a complex with topoisomerase II and DNA. This complex induces breaks in double stranded DNA and prevents repair by topoisomerase II binding. Accumulated breaks in DNA prevent entry into the mitotic phase of cell division, and lead to cell death. Etoposide acts primarily in the G2 and S phases of the cell cycle. [NIH]

Eukaryotic Cells: Cells of the higher organisms, containing a true nucleus bounded by a

nuclear membrane. [NIH]

Exanthema: Diseases in which skin eruptions or rashes are a prominent manifestation. Classically, six such diseases were described with similar rashes; they were numbered in the order in which they were reported. Only the fourth (Duke's disease), fifth (erythema infectiosum), and sixth (exanthema subitum) numeric designations survive as occasional synonyms in current terminology. [NIH]

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]

Exogenous: Developed or originating outside the organism, as exogenous disease. [EU]

Exon: The part of the DNA that encodes the information for the actual amino acid sequence of the protein. In many eucaryotic genes, the coding sequences consist of a series of exons alternating with intron sequences. [NIH]

Exophthalmos: Abnormal protrusion of both eyes; may be caused by endocrine gland malfunction, malignancy, injury, or paralysis of the extrinsic muscles of the eye. [NIH]

External-beam radiation: Radiation therapy that uses a machine to aim high-energy rays at the cancer. Also called external radiation. [NIH]

Extracellular: Outside a cell or cells. [EU]

Extracellular Matrix: A meshwork-like substance found within the extracellular space and in association with the basement membrane of the cell surface. It promotes cellular proliferation and provides a supporting structure to which cells or cell lysates in culture dishes adhere. [NIH]

Extraocular: External to or outside of the eye. [NIH]

Extremity: A limb; an arm or leg (membrum); sometimes applied specifically to a hand or foot. [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]

Febrile: Pertaining to or characterized by fever. [EU]

Fetus: The developing offspring from 7 to 8 weeks after conception until birth. [NIH]

Fibroblast Growth Factor: Peptide isolated from the pituitary gland and from the brain. It is a potent mitogen which stimulates growth of a variety of mesodermal cells including chondrocytes, granulosa, and endothelial cells. The peptide may be active in wound healing and animal limb regeneration. [NIH]

Fibroblasts: Connective tissue cells which secrete an extracellular matrix rich in collagen and other macromolecules. [NIH]

Fibronectin: An adhesive glycoprotein. One form circulates in plasma, acting as an opsonin; another is a cell-surface protein which mediates cellular adhesive interactions. [NIH]

Fibrosis: Any pathological condition where fibrous connective tissue invades any organ, usually as a consequence of inflammation or other injury. [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]

Fludarabine: An anticancer drug that belongs to the family of drugs called antimetabolites. [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]

Folate: A B-complex vitamin that is being studied as a cancer prevention agent. Also called folic acid. [NIH]

Fold: A plication or doubling of various parts of the body. [NIH]

Folic Acid: N-(4-(((2-Amino-1,4-dihydro-4-oxo-6-pteridinyl)methyl)amino)benzoyl)-L-glutamic acid. A member of the vitamin B family that stimulates the hematopoietic system. It is present in the liver and kidney and is found in mushrooms, spinach, yeast, green leaves, and grasses. Folic acid is used in the treatment and prevention of folate deficiencies and megaloblastic anemia. [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]

Fungemia: The presence of fungi circulating in the blood. Opportunistic fungal sepsis is seen most often in immunosuppressed patients with severe neutropenia or in postoperative patients with intravenous catheters and usually follows prolonged antibiotic therapy. [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]

Ganglion: 1. A knot, or knotlike mass. 2. A general term for a group of nerve cell bodies located outside the central nervous system; occasionally applied to certain nuclear groups within the brain or spinal cord, e.g. basal ganglia. 3. A benign cystic tumour occurring on a aponeurosis or tendon, as in the wrist or dorsum of the foot; it consists of a thin fibrous capsule enclosing a clear mucinous fluid. [EU]

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]

Gas exchange: Primary function of the lungs; transfer of oxygen from inhaled air into the blood and of carbon dioxide from the blood into the lungs. [NIH]

Gastric: Having to do with the stomach. [NIH]

Gemtuzumab ozogamicin: A type of monoclonal antibody used in cancer detection or therapy. Monoclonal antibodies are laboratory-produced substances that can locate and bind to cancer cells. [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 Dosage: The number of copies of a given gene present in a cell or nucleus. An increase in gene dosage can result in the formation of higher levels of gene product, provided that the gene is not subject to autogenous regulation. [NIH]

Gene Expression: The phenotypic manifestation of a gene or genes by the processes of gene action. [NIH]

Gene Expression Profiling: The determination of the pattern of genes expressed i.e., transcribed, under specific circumstances or in a specific cell. [NIH]

Gene Fusion: Fusion of structural genes to analyze protein behavior or fusion of regulatory sequences with structural genes to determine mechanisms of regulation. [NIH]

Gene Rearrangement: The ordered rearrangement of gene regions by DNA recombination such as that which occurs normally during development. [NIH]

Gene Silencing: Interruption or suppression of the expression of a gene at transcriptional or translational levels. [NIH]

Genes, Homeobox: Highly conserved DNA sequences which have been identified in specific gene transcripts ranging from those of Drosophila melanogaster to mouse and human. Homeobox genes function, in part, to generate DNA-binding proteins with an evolutionary conserved approximately 60-residue sequence (homeodomain proteins). [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 Screening: Searching a population or individuals for persons possessing certain genotypes or karyotypes that: (1) are already associated with disease or predispose to disease; (2) may lead to disease in their descendants; or (3) produce other variations not known to be associated with disease. Genetic screening may be directed toward identifying phenotypic expression of genetic traits. It includes prenatal genetic screening. [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]

Genetics: The biological science that deals with the phenomena and mechanisms of heredity. [NIH]

Genotype: The genetic constitution of the individual; the characterization of the genes. [NIH]

Germ cell tumors: Tumors that begin in the cells that give rise to sperm or eggs. They can occur virtually anywhere in the body and can be either benign or malignant. [NIH]

Germ Cells: The reproductive cells in multicellular organisms. [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]

Glucocorticoid: A compound that belongs to the family of compounds called corticosteroids (steroids). Glucocorticoids affect metabolism and have anti-inflammatory and

immunosuppressive effects. They may be naturally produced (hormones) or synthetic (drugs). [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]

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]

Glycoprotein: A protein that has sugar molecules attached to it. [NIH]

Governing Board: The group in which legal authority is vested for the control of health-related institutions and organizations. [NIH]

Grade: The grade of a tumor depends on how abnormal the cancer cells look under a microscope and how quickly the tumor is likely to grow and spread. Grading systems are different for each type of cancer. [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]

Graft-versus-host disease: GVHD. A reaction of donated bone marrow or peripheral stem cells against a person's tissue. [NIH]

Granulocyte: A type of white blood cell that fights bacterial infection. Neutrophils, eosinophils, and basophils are granulocytes. [NIH]

Granulocyte Colony-Stimulating Factor: A glycoprotein of MW 25 kDa containing internal disulfide bonds. It induces the survival, proliferation, and differentiation of neutrophilic granulocyte precursor cells and functionally activates mature blood neutrophils. Among the family of colony-stimulating factors, G-CSF is the most potent inducer of terminal differentiation to granulocytes and macrophages of leukemic myeloid cell lines. [NIH]

Granulocyte-Macrophage Colony-Stimulating Factor: An acidic glycoprotein of MW 23 kDa with internal disulfide bonds. The protein is produced in response to a number of inflammatory mediators by mesenchymal cells present in the hemopoietic environment and at peripheral sites of inflammation. GM-CSF is able to stimulate the production of neutrophilic granulocytes, macrophages, and mixed granulocyte-macrophage colonies from bone marrow cells and can stimulate the formation of eosinophil colonies from fetal liver progenitor cells. GM-CSF can also stimulate some functional activities in mature granulocytes and macrophages. [NIH]

Granulocytopenia: A deficiency in the number of granulocytes, a type of white blood cell. [NIH]

Gravis: Eruption of watery blisters on the skin among those handling animals and animal products. [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]

Guanylate Cyclase: An enzyme that catalyzes the conversion of GTP to 3',5'-cyclic GMP and pyrophosphate. It also acts on ITP and dGTP. (From Enzyme Nomenclature, 1992) EC 4.6.1.2. [NIH]

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]

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]

Hematologic malignancies: Cancers of the blood or bone marrow, including leukemia and lymphoma. Also called hematologic cancers. [NIH]

Hematology: A subspecialty of internal medicine concerned with morphology, physiology, and pathology of the blood and blood-forming tissues. [NIH]

Hematopoiesis: The development and formation of various types of blood cells. [NIH]

Hematopoietic growth factors: A group of proteins that cause blood cells to grow and mature. [NIH]

Hematopoietic Stem Cell Transplantation: The transference of stem cells from one animal or human to another (allogeneic), or within the same individual (autologous). The source for the stem cells may be the bone marrow or peripheral blood. Stem cell transplantation has been used as an alternative to autologous bone marrow transplantation in the treatment of a variety of neoplasms. [NIH]

Hematopoietic Stem Cells: Progenitor cells from which all blood cells derive. [NIH]

Hematopoietic tissue: Tissue in which new blood cells are formed. [NIH]

Hemochromatosis: A disease that occurs when the body absorbs too much iron. The body stores the excess iron in the liver, pancreas, and other organs. May cause cirrhosis of the liver. Also called iron overload disease. [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]

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]

Hemorrhage: Bleeding or escape of blood from a vessel. [NIH]

Hepatic: Refers to the liver. [NIH]

Hepatic Veins: Veins which drain the liver. [NIH]

Hepatic Veno-Occlusive Disease: Blockage of the small- or medium-sized hepatic veins due to nonthrombotic subendothelial edema which may progress to fibrosis. [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]

Hepatoma: A liver tumor. [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]

Heterodimer: Zippered pair of nonidentical proteins. [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]

Histiocytosis: General term for the abnormal appearance of histiocytes in the blood. Based on the pathological features of the cells involved rather than on clinical findings, the histiocytic diseases are subdivided into three groups: Langerhans cell histiocytosis, non-Langerhans cell histiocytosis, and malignant histiocytic disorders. [NIH]

Histocompatibility: The degree of antigenic similarity between the tissues of different individuals, which determines the acceptance or rejection of allografts. [NIH]

Histone Deacetylase: Hydrolyzes N-acetyl groups on histones. [NIH]

Histones: Small chromosomal proteins (approx 12-20 kD) possessing an open, unfolded structure and attached to the DNA in cell nuclei by ionic linkages. Classification into the various types (designated histone I, histone II, etc.) is based on the relative amounts of arginine and lysine in each. [NIH]

Homeobox: Distinctive sequence of DNA bases. [NIH]

Homeodomain Proteins: Proteins encoded by homeobox genes that exhibit structural similarity to certain prokaryotic and eukaryotic DNA-binding proteins. Homeodomain proteins are involved in the control of gene expression during morphogenesis and development (gene expression regulation, developmental). [NIH]

Homeotic: Characterizes genes the mutations of which lead to inappropriate expressions of characteristics normally associated with another part of the organism (homeotic mutants). [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]

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]

Hormone therapy: Treatment of cancer by removing, blocking, or adding hormones. Also called endocrine therapy. [NIH]

Hybrid: Cross fertilization between two varieties or, more usually, two species of vines, see also crossing. [NIH]

Hybridization: The genetic process of crossbreeding to produce a hybrid. Hybrid nucleic acids can be formed by nucleic acid hybridization of DNA and RNA molecules. Protein hybridization allows for hybrid proteins to be formed from polypeptide chains. [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]

Hyperbilirubinemia: Pathologic process consisting of an abnormal increase in the amount of bilirubin in the circulating blood, which may result in jaundice. [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]

Hypertrophy: General increase in bulk of a part or organ, not due to tumor formation, nor to an increase in the number of cells. [NIH]

Idarubicin: An orally administered anthracycline antibiotic. The compound has shown activity against breast cancer, lymphomas and leukemias, together with potential for reduced cardiac toxicity. [NIH]

Idiotype: The unique antigenic determinant in the variable region. [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]

Immunity: Nonsusceptibility to the invasive or pathogenic effects of foreign microorganisms or to the toxic effect of antigenic substances. [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]

Immunohistochemistry: Histochemical localization of immunoreactive substances using labeled antibodies as reagents. [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]

Immunophenotyping: Process of classifying cells of the immune system based on structural and functional differences. The process is commonly used to analyze and sort T-lymphocytes into subsets based on CD antigens by the technique of flow cytometry. [NIH]

Immunosuppressant: An agent capable of suppressing immune responses. [EU]

Immunosuppressive: Describes the ability to lower immune system responses. [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]

Immunotoxin: An antibody linked to a toxic substance. Some immmunotoxins can bind to cancer cells and kill them. [NIH]

Impairment: In the context of health experience, an impairment is any loss or abnormality of psychological, physiological, or anatomical structure or function. [NIH]

Implant radiation: A procedure in which radioactive material sealed in needles, seeds, wires, or catheters is placed directly into or near the tumor. Also called [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]

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]

Induction therapy: Treatment designed to be used as a first step toward shrinking the cancer and in evaluating response to drugs and other agents. Induction therapy is followed by additional therapy to eliminate whatever cancer remains. [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]

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]

Informed Consent: Voluntary authorization, given to the physician by the patient, with full comprehension of the risks involved, for diagnostic or investigative procedures and medical and surgical treatment. [NIH]

Infusion: A method of putting fluids, including drugs, into the bloodstream. Also called intravenous infusion. [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]

Insecticides: Pesticides designed to control insects that are harmful to man. The insects may be directly harmful, as those acting as disease vectors, or indirectly harmful, as destroyers of crops, food products, or textile fabrics. [NIH]

Insertional: A technique in which foreign DNA is cloned into a restriction site which occupies a position within the coding sequence of a gene in the cloning vector molecule. Insertion interrupts the gene's sequence such that its original function is no longer expressed. [NIH]

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]

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-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]

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-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]

Internal Medicine: A medical specialty concerned with the diagnosis and treatment of diseases of the internal organ systems of adults. [NIH]

Internal radiation: A procedure in which radioactive material sealed in needles, seeds, wires, or catheters is placed directly into or near the tumor. Also called brachytherapy, implant radiation, or interstitial radiation therapy. [NIH]

Interphase: The interval between two successive cell divisions during which the chromosomes are not individually distinguishable and DNA replication occurs. [NIH]

Interstitial: Pertaining to or situated between parts or in the interspaces of a tissue. [EU]

Intracellular: Inside a cell. [NIH]

Intravascular: Within a vessel or vessels. [EU]

Intravenous: IV. Into a vein. [NIH]

Intrinsic: Situated entirely within or pertaining exclusively to a part. [EU]

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]

Ionization: 1. Any process by which a neutral atom gains or loses electrons, thus acquiring a net charge, as the dissociation of a substance in solution into ions or ion production by the passage of radioactive particles. 2. Iontophoresis. [EU]

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]

Irradiation: The use of high-energy radiation from x-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 from materials called radioisotopes. Radioisotopes produce radiation and can be placed in or near the tumor or in the area near cancer cells. This type of radiation treatment is called internal radiation therapy, implant radiation, interstitial radiation, or brachytherapy. Systemic radiation therapy uses a radioactive substance, such as a radiolabeled monoclonal antibody, that circulates throughout the body. Irradiation is also called radiation therapy, radiotherapy, and x-ray therapy. [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]

Karyotype: The characteristic chromosome complement of an individual, race, or species as defined by their number, size, shape, etc. [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]

Killer Cells: Lymphocyte-like effector cells which mediate antibody-dependent cell cytotoxicity. They kill antibody-coated target cells which they bind with their Fc receptors. [NIH]

Kinetics: The study of rate dynamics in chemical or physical systems. [NIH]

Labile: 1. Gliding; moving from point to point over the surface; unstable; fluctuating. 2. Chemically unstable. [EU]

Laminin: Large, noncollagenous glycoprotein with antigenic properties. It is localized in the basement membrane lamina lucida and functions to bind epithelial cells to the basement membrane. Evidence suggests that the protein plays a role in tumor invasion. [NIH]

Latency: The period of apparent inactivity between the time when a stimulus is presented and the moment a response occurs. [NIH]

Latent: Phoria which occurs at one distance or another and which usually has no troublesome effect. [NIH]

Lentivirus: A genus of the family Retroviridae consisting of non-oncogenic retroviruses that produce multi-organ diseases characterized by long incubation periods and persistent infection. Lentiviruses are unique in that they contain open reading frames (ORFs) between the pol and env genes and in the 3' env region. Five serogroups are recognized, reflecting the mammalian hosts with which they are associated. HIV-1 is the type species. [NIH]

Lesion: An area of abnormal tissue change. [NIH]

Lethal: Deadly, fatal. [EU]

Leucine: An essential branched-chain amino acid important for hemoglobin formation. [NIH]

Leucocyte: All the white cells of the blood and their precursors (myeloid cell series, lymphoid cell series) but commonly used to indicate granulocytes exclusive of lymphocytes. [NIH]

Leukaemia: An acute or chronic disease of unknown cause in man and other warm-blooded animals that involves the blood-forming organs, is characterized by an abnormal increase in the number of leucocytes in the tissues of the body with or without a corresponding increase of those in the circulating blood, and is classified according of the type leucocyte most prominently involved. [EU]

Leukemia: Cancer of blood-forming tissue. [NIH]

Levo: It is an experimental treatment for heroin addiction that was developed by German scientists around 1948 as an analgesic. Like methadone, it binds with opioid receptors, but it is longer acting. [NIH]

Ligands: A RNA simulation method developed by the MIT. [NIH]

Ligation: Application of a ligature to tie a vessel or strangulate a part. [NIH]

Light microscope: A microscope (device to magnify small objects) in which objects are lit directly by white light. [NIH]

Linkages: 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]

Lipid: Fat. [NIH]

Liposomal: A drug preparation that contains the active drug in very tiny fat particles. This fat-encapsulated drug is absorbed better, and its distribution to the tumor site is improved. [NIH]

Liposome: A spherical particle in an aqueous medium, formed by a lipid bilayer enclosing an aqueous compartment. [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 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]

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]

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]

Lovastatin: A fungal metabolite isolated from cultures of Aspergillus terreus. The compound is a potent anticholesteremic agent. It inhibits 3-hydroxy-3-methylglutaryl coenzyme A reductase (hydroxymethylglutaryl CoA reductases), which is the rate-limiting enzyme in cholesterol biosynthesis. It also stimulates the production of low-density lipoprotein receptors in the liver. [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]

Lucida: An instrument, invented by Wollaton, consisting essentially of a prism or a mirror through which an object can be viewed so as to appear on a plane surface seen in direct view and on which the outline of the object may be traced. [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]

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]

Lymphadenopathy: Disease or swelling of the lymph nodes. [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]

Lymphoblastic: One of the most aggressive types of non-Hodgkin lymphoma. [NIH]

Lymphoblasts: Interferon produced predominantly by leucocyte cells. [NIH]

Lymphocytes: White blood cells formed in the body's lymphoid tissue. The nucleus is round or ovoid with coarse, irregularly clumped chromatin while the cytoplasm is typically pale blue with azurophilic (if any) granules. Most lymphocytes can be classified as either T or B (with subpopulations of each); those with characteristics of neither major class are called null cells. [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]

Lysine: An essential amino acid. It is often added to animal feed. [NIH]

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]

Macrophage Colony-Stimulating Factor: A mononuclear phagocyte colony-stimulating factor synthesized by mesenchymal cells. The compound stimulates the survival, proliferation, and differentiation of hematopoietic cells of the monocyte-macrophage series. M-CSF is a disulfide-bonded glycoprotein dimer with a MW of 70 kDa. It binds to a specific high affinity receptor (receptor, macrophage colony-stimulating factor). [NIH]

Maculopapular: Both macular and papular, as an eruption consisting of both macules and papules; sometimes erroneously used to designate a papule that is only slightly elevated. [EU]

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]

Mammary: Pertaining to the mamma, or breast. [EU]

Maximum Tolerated Dose: The highest dose level eliciting signs of toxicity without having major effects on survival relative to the test in which it is used. [NIH]

Median survival time: The point in time from either diagnosis or treatment at which half of the patients with a given disease are found to be, or expected to be, still alive. In a clinical trial, median survival time is one way to measure how effective a treatment is. [NIH]

Mediate: Indirect; accomplished by the aid of an intervening medium. [EU]

Mediator: An object or substance by which something is mediated, such as (1) a structure of the nervous system that transmits impulses eliciting a specific response; (2) a chemical substance (transmitter substance) that induces activity in an excitable tissue, such as nerve or muscle; or (3) a substance released from cells as the result of the interaction of antigen with antibody or by the action of antigen with a sensitized lymphocyte. [EU]

MEDLINE: An online database of MEDLARS, the computerized bibliographic Medical Literature Analysis and Retrieval System of the National Library of Medicine. [NIH]

Medulloblastoma: A malignant brain tumor that begins in the lower part of the brain and can spread to the spine or to other parts of the body. Medulloblastomas are sometimes called primitive neuroectodermal tumors (PNET). [NIH]

Megakaryocytes: Very large bone marrow cells which release mature blood platelets. [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]

Melphalan: An alkylating nitrogen mustard that is used as an antineoplastic in the form of the levo isomer - melphalan, the racemic mixture - merphalan, and the dextro isomer - medphalan; toxic to bone marrow, but little vesicant action; potential carcinogen. [NIH]

Membrane: A very thin layer of tissue that covers a surface. [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]

Meningeal: Refers to the meninges, the tissue covering the brain and spinal cord. [NIH]

Meninges: The three membranes that cover and protect the brain and spinal cord. [NIH]

Meningitis: Inflammation of the meninges. When it affects the dura mater, the disease is termed pachymeningitis; when the arachnoid and pia mater are involved, it is called leptomeningitis, or meningitis proper. [EU]

Menstrual Cycle: The period of the regularly recurring physiologic changes in the endometrium occurring during the reproductive period in human females and some primates and culminating in partial sloughing of the endometrium (menstruation). [NIH]

Mental: Pertaining to the mind; psychic. 2. (L. mentum chin) pertaining to the chin. [EU]

Mental Retardation: Refers to sub-average general intellectual functioning which originated during the developmental period and is associated with impairment in adaptive behavior. [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]

Mesenchymal: Refers to cells that develop into connective tissue, blood vessels, and lymphatic tissue. [NIH]

Meta-Analysis: A quantitative method of combining the results of independent studies (usually drawn from the published literature) and synthesizing summaries and conclusions which may be used to evaluate therapeutic effectiveness, plan new studies, etc., with application chiefly in the areas of research and medicine. [NIH]

Metabolite: Any substance produced by metabolism or by a metabolic process. [EU]

Metastasis: The spread of cancer from one part of the body to another. Tumors formed from cells that have spread are called "secondary tumors" and contain cells that are like those in the original (primary) tumor. The plural is metastases. [NIH]

Methyltransferase: A drug-metabolizing enzyme. [NIH]

Microbe: An organism which cannot be observed with the naked eye; e. g. unicellular animals, lower algae, lower fungi, bacteria. [NIH]

Micronutrients: Essential dietary elements or organic compounds that are required in only small quantities for normal physiologic processes to occur. [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]

Microscopy: The application of microscope magnification to the study of materials that cannot be properly seen by the unaided eye. [NIH]

Microtubules: Slender, cylindrical filaments found in the cytoskeleton of plant and animal cells. They are composed of the protein tubulin. [NIH]

Migration: The systematic movement of genes between populations of the same species, geographic race, or variety. [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]

Mitotic: Cell resulting from mitosis. [NIH]

Mitotic Spindle Apparatus: An organelle consisting of three components: (1) the astral microtubules, which form around each centrosome and extend to the periphery; (2) the polar microtubules which extend from one spindle pole to the equator; and (3) the kinetochore microtubules, which connect the centromeres of the various chromosomes to either centrosome. [NIH]

Mitoxantrone: An anthracenedione-derived antineoplastic agent. [NIH]

Mobility: Capability of movement, of being moved, or of flowing freely. [EU]

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]

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]

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]

Motor nerve: An efferent nerve conveying an impulse that excites muscular contraction. [NIH]

Multidrug resistance: Adaptation of tumor cells to anticancer drugs in ways that make the drugs less effective. [NIH]

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]

Muscle relaxant: An agent that specifically aids in reducing muscle tension, as those acting at the polysynaptic neurons of motor nerves (e.g. meprobamate) or at the myoneural junction (curare and related compounds). [EU]

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]

Mutagenic: Inducing genetic mutation. [EU]

Myasthenia: Muscular debility; any constitutional anomaly of muscle. [EU]

Myelodysplasia: Abnormal bone marrow cells that may lead to myelogenous leukemia. [NIH]

Myelodysplastic Syndromes: Conditions in which the bone marrow shows qualitative and quantitative changes suggestive of a preleukemic process, but having a chronic course that does not necessarily terminate as acute leukemia. [NIH]

Myelogenous: Produced by, or originating in, the bone marrow. [NIH]

Myeloid Cells: Cells which include the monocytes and the granulocytes. [NIH]

Myeloid Progenitor Cells: One of the two stem cells derived from hematopoietic stem cells - the other being the lymphoid progenitor cell. Derived from these myeloid progenitor cells are the erythroid progenitor cells and the myeloid cells (monocytes and granulocytes). [NIH]

Myeloma: Cancer that arises in plasma cells, a type of white blood cell. [NIH]

Myeloproliferative Disorders: Disorders in which one or more stimuli cause proliferation of hemopoietically active tissue or of tissue which has embryonic hemopoietic potential. [NIH]

Myelosuppression: A condition in which bone marrow activity is decreased, resulting in fewer red blood cells, white blood cells, and platelets. Myelosuppression is a side effect of some cancer treatments. [NIH]

Myocarditis: Inflammation of the myocardium; inflammation of the muscular walls of the heart. [EU]

Natural killer cells: NK cells. A type of white blood cell that contains granules with enzymes that can kill tumor cells or microbial cells. Also called large granular lymphocytes (LGL). [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]

Neoplasia: Abnormal and uncontrolled cell growth. [NIH]

Neoplasm: A new growth of benign or malignant tissue. [NIH]

Neostigmine: A cholinesterase inhibitor used in the treatment of myasthenia gravis and to reverse the effects of muscle relaxants such as gallamine and tubocurarine. Neostigmine, unlike physostigmine, does not cross the blood-brain barrier. [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]

Neuroblastoma: Cancer that arises in immature nerve cells and affects mostly infants and children. [NIH]

Neurosyphilis: A late form of syphilis that affects the brain and may lead to dementia and death. [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]

Neutrons: Electrically neutral elementary particles found in all atomic nuclei except light hydrogen; the mass is equal to that of the proton and electron combined and they are unstable when isolated from the nucleus, undergoing beta decay. Slow, thermal, epithermal,

and fast neutrons refer to the energy levels with which the neutrons are ejected from heavier nuclei during their decay. [NIH]

Neutropenia: An abnormal decrease in the number of neutrophils, a type of white blood cell. [NIH]

Neutrophil: A type of white blood cell. [NIH]

Nitric Oxide: A free radical gas produced endogenously by a variety of mammalian cells. It is synthesized from arginine by a complex reaction, catalyzed by nitric oxide synthase. Nitric oxide is endothelium-derived relaxing factor. It is released by the vascular endothelium and mediates the relaxation induced by some vasodilators such as acetylcholine and bradykinin. It also inhibits platelet aggregation, induces disaggregation of aggregated platelets, and inhibits platelet adhesion to the vascular endothelium. Nitric oxide activates cytosolic guanylate cyclase and thus elevates intracellular levels of cyclic GMP. [NIH]

Nitrogen: An element with the atomic symbol N, atomic number 7, and atomic weight 14. Nitrogen exists as a diatomic gas and makes up about 78% of the earth's atmosphere by volume. It is a constituent of proteins and nucleic acids and found in all living cells. [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]

Nuclear Envelope: The membrane system of the cell nucleus that surrounds the nucleoplasm. It consists of two concentric membranes separated by the perinuclear space. The structures of the envelope where it opens to the cytoplasm are called the nuclear pores (nuclear pore). [NIH]

Nuclear Pore: An opening through the nuclear envelope formed by the nuclear pore complex which transports nuclear proteins or RNA into or out of the cell nucleus and which, under some conditions, acts as an ion channel. [NIH]

Nuclear Proteins: Proteins found in the nucleus of a cell. Do not confuse with nucleoproteins which are proteins conjugated with nucleic acids, that are not necessarily present in the nucleus. [NIH]

Nucleates: Bacteria-inducing ice nucleation at warm temperatures (between zero and minus ten degrees C.). [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]

Nucleic Acid Hybridization: The process whereby two single-stranded polynucleotides form a double-stranded molecule, with hydrogen bonding between the complementary bases in the two strains. [NIH]

Nucleoli: 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]

Nucleoproteins: Proteins conjugated with nucleic acids. [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]

Oculomotor: Cranial nerve III. It originate from the lower ventral surface of the midbrain and is classified as a motor nerve. [NIH]

Oculomotor Nerve: The 3d cranial nerve. The oculomotor nerve sends motor fibers to the levator muscles of the eyelid and to the superior rectus, inferior rectus, and inferior oblique muscles of the eye. It also sends parasympathetic efferents (via the ciliary ganglion) to the muscles controlling pupillary constriction and accommodation. The motor fibers originate in the oculomotor nuclei of the midbrain. [NIH]

Odds Ratio: The ratio of two odds. The exposure-odds ratio for case control data is the ratio of the odds in favor of exposure among cases to the odds in favor of exposure among noncases. The disease-odds ratio for a cohort or cross section is the ratio of the odds in favor of disease among the exposed to the odds in favor of disease among the unexposed. The prevalence-odds ratio refers to an odds ratio derived cross-sectionally from studies of prevalent cases. [NIH]

Oligonucleotide Probes: Synthetic or natural oligonucleotides used in hybridization studies in order to identify and study specific nucleic acid fragments, e.g., DNA segments near or within a specific gene locus or gene. The probe hybridizes with a specific mRNA, if present. Conventional techniques used for testing for the hybridization product include dot blot assays, Southern blot assays, and DNA:RNA hybrid-specific antibody tests. Conventional labels for the probe include the radioisotope labels 32P and 125I and the chemical label biotin. [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]

Oncogenic: Chemical, viral, radioactive or other agent that causes cancer; carcinogenic. [NIH]

Oncology: The study of cancer. [NIH]

Open Reading Frames: Reading frames where successive nucleotide triplets can be read as codons specifying amino acids and where the sequence of these triplets is not interrupted by stop codons. [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]

Orbit: One of the two cavities in the skull which contains an eyeball. Each eye is located in a bony socket or orbit. [NIH]

Orbital: Pertaining to the orbit (= the bony cavity that contains the eyeball). [EU]

Orderly: A male hospital attendant. [NIH]

Osteogenic sarcoma: A malignant tumor of the bone. Also called osteosarcoma. [NIH]

Osteosarcoma: A cancer of the bone that affects primarily children and adolescents. Also called osteogenic sarcoma. [NIH]

Overall survival: The percentage of subjects in a study who have survived for a defined period of time. Usually reported as time since diagnosis or treatment. Often called the survival rate. [NIH]

Overexpress: An excess of a particular protein on the surface of a cell. [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]

P53 gene: A tumor suppressor gene that normally inhibits the growth of tumors. This gene is altered in many types of cancer. [NIH]

Pachymeningitis: Inflammation of the dura mater of the brain, the spinal cord or the optic nerve. [NIH]

Paclitaxel: Antineoplastic agent isolated from the bark of the Pacific yew tree, Taxus brevifolia. Paclitaxel stabilizes microtubules in their polymerized form and thus mimics the action of the proto-oncogene proteins c-mos. [NIH]

Paediatric: Of or relating to the care and medical treatment of children; belonging to or concerned with paediatrics. [EU]

Palliative: 1. Affording relief, but not cure. 2. An alleviating medicine. [EU]

Palsy: Disease of the peripheral nervous system occurring usually after many years of increased lead absorption. [NIH]

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]

Pancytopenia: Deficiency of all three cell elements of the blood, erythrocytes, leukocytes and platelets. [NIH]

Papule: A small circumscribed, superficial, solid elevation of the skin. [EU]

Paralysis: Loss of ability to move all or part of the body. [NIH]

Paraparesis: Mild to moderate loss of bilateral lower extremity motor function, which may be a manifestation of spinal cord diseases; peripheral nervous system diseases; muscular diseases; intracranial hypertension; parasagittal brain lesions; and other conditions. [NIH]

Paresis: A general term referring to a mild to moderate degree of muscular weakness, occasionally used as a synonym for paralysis (severe or complete loss of motor function). In the older literature, paresis often referred specifically to paretic neurosyphilis. "General paresis" and "general paralysis" may still carry that connotation. Bilateral lower extremity paresis is referred to as paraparesis. [NIH]

Partial remission: The shrinking, but not complete disappearance, of a tumor in response to therapy. Also called partial response. [NIH]

Particle: A tiny mass of material. [EU]

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]

Peer Review: An organized procedure carried out by a select committee of professionals in evaluating the performance of other professionals in meeting the standards of their specialty. Review by peers is used by editors in the evaluation of articles and other papers submitted for publication. Peer review is used also in the evaluation of grant applications. It

is applied also in evaluating the quality of health care provided to patients. [NIH]

Peptide: Any compound consisting of two or more amino acids, the building blocks of proteins. Peptides are combined to make proteins. [NIH]

Peripheral blood: Blood circulating throughout the body. [NIH]

Peripheral Nervous System: The nervous system outside of the brain and spinal cord. The peripheral nervous system has autonomic and somatic divisions. The autonomic nervous system includes the enteric, parasympathetic, and sympathetic subdivisions. The somatic nervous system includes the cranial and spinal nerves and their ganglia and the peripheral sensory receptors. [NIH]

Peripheral stem cells: Immature cells found circulating in the bloodstream. New blood cells develop from peripheral stem cells. [NIH]

Pesticides: Chemicals used to destroy pests of any sort. The concept includes fungicides (industrial fungicides), insecticides, rodenticides, etc. [NIH]

Phagocyte: An immune system cell that can surround and kill microorganisms and remove dead cells. Phagocytes include macrophages. [NIH]

Phagocytosis: The engulfing of microorganisms, other cells, and foreign particles by phagocytic cells. [NIH]

Pharmacodynamic: Is concerned with the response of living tissues to chemical stimuli, that is, the action of drugs on the living organism in the absence of disease. [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]

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]

Phospholipases: A class of enzymes that catalyze the hydrolysis of phosphoglycerides or glycerophosphatidates. EC 3.1.-. [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]

Phosphorylates: 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]

Photoreceptors: Cells specialized to detect and transduce light. [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]

Physostigmine: A cholinesterase inhibitor that is rapidly absorbed through membranes. It can be applied topically to the conjunctiva. It also can cross the blood-brain barrier and is used when central nervous system effects are desired, as in the treatment of severe anticholinergic toxicity. [NIH]

Phytotoxin: A substance which is toxic for plants. [NIH]

Pilot study: The initial study examining a new method or treatment. [NIH]

Pituitary Gland: A small, unpaired gland situated in the sella turcica tissue. It is connected to the hypothalamus by a short stalk. [NIH]

Placenta: A highly vascular fetal organ through which the fetus absorbs oxygen and other nutrients and excretes carbon dioxide and other wastes. It begins to form about the eighth day of gestation when the blastocyst adheres to the decidua. [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]

Platelet Activation: A series of progressive, overlapping events triggered by exposure of the platelets to subendothelial tissue. These events include shape change, adhesiveness, aggregation, and release reactions. When carried through to completion, these events lead to the formation of a stable hemostatic plug. [NIH]

Platelet Aggregation: The attachment of platelets to one another. This clumping together can be induced by a number of agents (e.g., thrombin, collagen) and is part of the mechanism leading to the formation of a thrombus. [NIH]

Platelet Transfusion: The transfer of blood platelets from a donor to a recipient or reinfusion to the donor. [NIH]

Platelets: A type of blood cell that helps prevent bleeding by causing blood clots to form. Also called thrombocytes. [NIH]

Pneumonia: Inflammation of the lungs. [NIH]

Podophyllotoxin: The main active constituent of the resin from the roots of may apple or mandrake (Podophyllum peltatum and P. emodi). It is a potent spindle poison, toxic if taken internally, and has been used as a cathartic. It is very irritating to skin and mucous membranes, has keratolytic actions, has been used to treat warts and keratoses, and may have antineoplastic properties, as do some of its congeners and derivatives. [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]

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]

Polyneuritis: Inflammation of several peripheral nerves at the same time. [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]

Postnatal: Occurring after birth, with reference to the newborn. [EU]

Postoperative: After surgery. [NIH]

Postremission therapy: Anticancer drugs to kill cancer cells that survive after remission induction therapy. [NIH]

Postsynaptic: Nerve potential generated by an inhibitory hyperpolarizing stimulation. [NIH]

Potentiates: A degree of synergism which causes the exposure of the organism to a harmful substance to worsen a disease already contracted. [NIH]

Potentiation: An overall effect of two drugs taken together which is greater than the sum of the effects of each drug taken alone. [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]

Precancerous: A term used to describe a condition that may (or is likely to) become cancer. Also called premalignant. [NIH]

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]

Predisposition: A latent susceptibility to disease which may be activated under certain conditions, as by stress. [EU]

Premalignant: A term used to describe a condition that may (or is likely to) become cancer. Also called precancerous. [NIH]

Prenatal: Existing or occurring before birth, with reference to the fetus. [EU]

Primary tumor: The original tumor. [NIH]

Primitive neuroectodermal tumors: PNET. A type of bone cancer that forms in the middle (shaft) of large bones. Also called Ewing's sarcoma/primitive neuroectodermal tumor. [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]

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]

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]

Promyelocytic leukemia: A type of acute myeloid leukemia, a quickly progressing disease in which too many immature blood-forming cells are found in the blood and bone marrow. [NIH]

Prophylaxis: An attempt to prevent disease. [NIH]

Proptosis: Forward projection or displacement especially of the eyeball : exophthalmos. [EU]

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]

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]

Protein Transport: The process of moving proteins from one cellular compartment (including extracellular) to another by various sorting and transport mechanisms such as gated transport, protein translocation, and vesicular transport. [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]

Proto-Oncogene Proteins: Products of proto-oncogenes. Normally they do not have oncogenic or transforming properties, but are involved in the regulation or differentiation of cell growth. They often have protein kinase activity. [NIH]

Proto-Oncogene Proteins c-mos: Cellular proteins encoded by the c-mos genes. They function in the cell cycle to maintain maturation promoting factor in the active state and have protein-serine/threonine kinase activity. Oncogenic transformation can take place when c-mos proteins are expressed at the wrong time. [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]

Proviruses: Duplex DNA sequences in eukaryotic chromosomes, corresponding to the genome of a virus, that are transmitted from one cell generation to the next without causing lysis of the host. Proviruses are often associated with neoplastic cell transformation and are key features of retrovirus biology. [NIH]

Proximal: Nearest; closer to any point of reference; opposed to distal. [EU]

Psychic: Pertaining to the psyche or to the mind; mental. [EU]

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]

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]

Quality of Health Care: The levels of excellence which characterize the health service or health care provided based on accepted standards of quality. [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]

Racemic: Optically inactive but resolvable in the way of all racemic compounds. [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]

Radioisotope: An unstable element that releases radiation as it breaks down. Radioisotopes can be used in imaging tests or as a treatment for cancer. [NIH]

Radiolabeled: Any compound that has been joined with a radioactive substance. [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]

Random Allocation: A process involving chance used in therapeutic trials or other research endeavor for allocating experimental subjects, human or animal, between treatment and control groups, or among treatment groups. It may also apply to experiments on inanimate objects. [NIH]

Randomization: Also called random allocation. Is allocation of individuals to groups, e.g., for experimental and control regimens, by chance. Within the limits of chance variation, random allocation should make the control and experimental groups similar at the start of an investigation and ensure that personal judgment and prejudices of the investigator do not influence allocation. [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]

Randomized clinical trial: A study in which the participants are assigned by chance to separate groups that compare different treatments; neither the researchers nor the participants can choose which group. Using chance to assign people to groups means that the groups will be similar and that the treatments they receive can be compared objectively. At the time of the trial, it is not known which treatment is best. It is the patient's choice to be in a randomized trial. [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]

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]

Reductase: Enzyme converting testosterone to dihydrotestosterone. [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]

Relative risk: The ratio of the incidence rate of a disease among individuals exposed to a specific risk factor to the incidence rate among unexposed individuals; synonymous with risk ratio. Alternatively, the ratio of the cumulative incidence rate in the exposed to the cumulative incidence rate in the unexposed (cumulative incidence ratio). The term relative risk has also been used synonymously with odds ratio. This is because the odds ratio and relative risk approach each other if the disease is rare (5 percent of population) and the number of subjects is large. [NIH]

Relative survival rate: A specific measurement of survival. In cancer, the rate is calculated by adjusting the survival rate to remove all causes of death except cancer. The rate is determined at specific time intervals, such as 2 years and 5 years after diagnosis. [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]

Remission Induction: Therapeutic act or process that initiates a response to a complete or partial remission level. [NIH]

Remission induction therapy: The initial chemotherapy a person receives to bring about a remission. [NIH]

Renal failure: Progressive renal insufficiency and uremia, due to irreversible and progressive renal glomerular tubular or interstitial disease. [NIH]

Repressor: Any of the specific allosteric protein molecules, products of regulator genes, which bind to the operator of operons and prevent RNA polymerase from proceeding into

the operon to transcribe messenger RNA. [NIH]

Repressor Proteins: Proteins which are normally bound to the operator locus of an operon, thereby preventing transcription of the structural genes. In enzyme induction, the substrate of the inducible enzyme binds to the repressor protein, causing its release from the operator and freeing the structural genes for transcription. In enzyme repression, the end product of the enzyme sequence binds to the free repressor protein, the resulting complex then binds to the operator and prevents transcription of the structural genes. [NIH]

Reproductive cells: Egg and sperm cells. Each mature reproductive cell carries a single set of 23 chromosomes. [NIH]

Research Support: Financial support of research activities. [NIH]

Residual disease: Cancer cells that remain after attempts have been made to remove the cancer. [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]

Respiratory failure: Inability of the lungs to conduct gas exchange. [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]

Retinoids: Derivatives of vitamin A. Used clinically in the treatment of severe cystic acne, psoriasis, and other disorders of keratinization. Their possible use in the prophylaxis and treatment of cancer is being actively explored. [NIH]

Retinol: Vitamin A. It is essential for proper vision and healthy skin and mucous membranes. Retinol is being studied for cancer prevention; it belongs to the family of drugs called retinoids. [NIH]

Retinyl palmitate: A drug being studied in cancer prevention; it belongs to the family of drugs called retinoids. [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]

Retrovirus: A member of a group of RNA viruses, the RNA of which is copied during viral replication into DNA by reverse transcriptase. The viral DNA is then able to be integrated into the host chromosomal DNA. [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]

Rhabdomyosarcoma: A malignant tumor of muscle tissue. [NIH]

Ribonuclease: RNA-digesting enzyme. [NIH]

Ribose: A pentose active in biological systems usually in its D-form. [NIH]

Ricin: A protein phytotoxin from the seeds of Ricinus communis, the castor oil plant. It agglutinates cells, is proteolytic, and causes lethal inflammation and hemorrhage if taken internally. [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]

Risk factor: A habit, trait, condition, or genetic alteration that increases a person's chance of developing a disease. [NIH]

Rodenticides: Substances used to destroy or inhibit the action of rats, mice, or other rodents. [NIH]

Rods: One type of specialized light-sensitive cells (photoreceptors) in the retina that provide side vision and the ability to see objects in dim light (night vision). [NIH]

Sabin: The unit of acoustic absorption. One Sabin is 1 sq. foot of perfect sound-absorbing material. [NIH]

Sarcoma: A connective tissue neoplasm formed by proliferation of mesodermal cells; it is usually highly malignant. [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]

Semisynthetic: Produced by chemical manipulation of naturally occurring substances. [EU]

Sepsis: The presence of bacteria in the bloodstream. [NIH]

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]

Sequence Homology: The degree of similarity between sequences. Studies of amino acid and nucleotide sequences provide useful information about the genetic relatedness of certain species. [NIH]

Sequencing: The determination of the order of nucleotides in a DNA or RNA chain. [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]

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]

Signal Transduction: The intercellular or intracellular transfer of information (biological activation/inhibition) through a signal pathway. In each signal transduction system, an activation/inhibition signal from a biologically active molecule (hormone, neurotransmitter) is mediated via the coupling of a receptor/enzyme to a second messenger system or to an ion channel. Signal transduction plays an important role in activating cellular functions, cell

differentiation, and cell proliferation. Examples of signal transduction systems are the GABA-postsynaptic receptor-calcium ion channel system, the receptor-mediated T-cell activation pathway, and the receptor-mediated activation of phospholipases. Those coupled to membrane depolarization or intracellular release of calcium include the receptor-mediated activation of cytotoxic functions in granulocytes and the synaptic potentiation of protein kinase activation. Some signal transduction pathways may be part of larger signal transduction pathways; for example, protein kinase activation is part of the platelet activation signal pathway. [NIH]

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]

Skeleton: The framework that supports the soft tissues of vertebrate animals and protects many of their internal organs. The skeletons of vertebrates are made of bone and/or cartilage. [NIH]

Social Environment: The aggregate of social and cultural institutions, forms, patterns, and processes that influence the life of an individual or community. [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]

Soma: The body as distinct from the mind; all the body tissue except the germ cells; all the axial body. [NIH]

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]

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]

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]

Sporadic: Neither endemic nor epidemic; occurring occasionally in a random or isolated manner. [EU]

Standard therapy: A currently accepted and widely used treatment for a certain type of cancer, based on the results of past research. [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]

Sterility: 1. The inability to produce offspring, i.e., the inability to conceive (female s.) or to induce conception (male s.). 2. The state of being aseptic, or free from microorganisms. [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]

Stool: The waste matter discharged in a bowel movement; feces. [NIH]

Strand: DNA normally exists in the bacterial nucleus in a helix, in which two strands are coiled together. [NIH]

Streptococcal: Caused by infection due to any species of streptococcus. [NIH]

Streptococcus: A genus of gram-positive, coccoid bacteria whose organisms occur in pairs or chains. No endospores are produced. Many species exist as commensals or parasites on man or animals with some being highly pathogenic. A few species are saprophytes and occur in the natural environment. [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]

Stromal: Large, veil-like cell in the bone marrow. [NIH]

Stromal Cells: Connective tissue cells of an organ found in the loose connective tissue. These are most often associated with the uterine mucosa and the ovary as well as the hematopoietic system and elsewhere. [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]

Submaxillary: Four to six lymph glands, located between the lower jaw and the submandibular salivary gland. [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]

Supplementation: Adding nutrients to the diet. [NIH]

Suppression: A conscious exclusion of disapproved desire contrary with repression, in which the process of exclusion is not conscious. [NIH]

Surface Plasmon Resonance: A biosensing technique in which biomolecules capable of binding to specific analytes or ligands are first immobilized on one side of a metallic film. Light is then focused on the opposite side of the film to excite the surface plasmons, that is, the oscillations of free electrons propagating along the film's surface. The refractive index of light reflecting off this surface is measured. When the immobilized biomolecules are bound by their ligands, an alteration in surface plasmons on the opposite side of the film is created which is directly proportional to the change in bound, or adsorbed, mass. Binding is measured by changes in the refractive index. The technique is used to study biomolecular

interactions, such as antigen-antibody binding. [NIH]

Survival Rate: The proportion of survivors in a group, e.g., of patients, studied and followed over a period, or the proportion of persons in a specified group alive at the beginning of a time interval who survive to the end of the interval. It is often studied using life table methods. [NIH]

Synaptic: Pertaining to or affecting a synapse (= site of functional apposition between neurons, at which an impulse is transmitted from one neuron to another by electrical or chemical means); pertaining to synapsis (= pairing off in point-for-point association of homologous chromosomes from the male and female pronuclei during the early prophase of meiosis). [EU]

Synergistic: Acting together; enhancing the effect of another force or agent. [EU]

Systemic: Affecting the entire body. [NIH]

Testosterone: A hormone that promotes the development and maintenance of male sex characteristics. [NIH]

Tetracycline: An antibiotic originally produced by Streptomyces viridifaciens, but used mostly in synthetic form. It is an inhibitor of aminoacyl-tRNA binding during protein synthesis. [NIH]

Theophylline: Alkaloid obtained from Thea sinensis (tea) and others. It stimulates the heart and central nervous system, dilates bronchi and blood vessels, and causes diuresis. The drug is used mainly in bronchial asthma and for myocardial stimulation. Among its more prominent cellular effects are inhibition of cyclic nucleotide phosphodiesterases and antagonism of adenosine receptors. [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]

Thioguanine: An antineoplastic compound which also has antimetabolite action. The drug is used in the therapy of acute leukemia. [NIH]

Threshold: For a specified sensory modality (e. g. light, sound, vibration), the lowest level (absolute threshold) or smallest difference (difference threshold, difference limen) or intensity of the stimulus discernible in prescribed conditions of stimulation. [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]

Thrombocytosis: Increased numbers of platelets in the peripheral blood. [EU]

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]

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]

Tissue: A group or layer of cells that are alike in type and work together to perform a specific function. [NIH]

Tissue Banks: Centers for acquiring, characterizing, and storing organs or tissue for future

use. [NIH]

Tonicity: The normal state of muscular tension. [NIH]

Topical: On the surface of the body. [NIH]

Topotecan: An antineoplastic agent used to treat ovarian cancer. It works by inhibiting DNA topoisomerase. [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]

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]

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]

Transmitter: A chemical substance which effects the passage of nerve impulses from one cell to the other at the synapse. [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 Failure: A measure of the quality of health care by assessment of unsuccessful results of management and procedures used in combating disease, in individual cases or series. [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]

Trisomy: The possession of a third chromosome of any one type in an otherwise diploid cell. [NIH]

Tuberculosis: Any of the infectious diseases of man and other animals caused by species of Mycobacterium. [NIH]

Tubocurarine: A neuromuscular blocker and active ingredient in curare; plant based alkaloid of Menispermaceae. [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 model: A type of animal model which can be 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]

Tumor suppressor gene: Genes in the body that can suppress or block the development of cancer. [NIH]

Tumorigenic: Chemical, viral, radioactive or other agent that causes cancer; carcinogenic. [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]

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]

Ubiquitin: A highly conserved 76 amino acid-protein found in all eukaryotic cells. [NIH]

Uracil: An anticancer drug that belongs to the family of drugs called alkylating agents. [NIH]

Uremia: The illness associated with the buildup of urea in the blood because the kidneys are not working effectively. Symptoms include nausea, vomiting, loss of appetite, weakness, and mental confusion. [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]

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]

Vaccine: A substance or group of substances meant to cause the immune system to respond to a tumor or to microorganisms, such as bacteria or viruses. [NIH]

Vagina: The muscular canal extending from the uterus to the exterior of the body. Also called the birth canal. [NIH]

Vascular: Pertaining to blood vessels or indicative of a copious blood supply. [EU]

Vascular endothelial growth factor: VEGF. A substance made by cells that stimulates new blood vessel formation. [NIH]

Vasodilators: Any nerve or agent which induces dilatation of the blood vessels. [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]

Venous: Of or pertaining to the veins. [EU]

Ventral: 1. Pertaining to the belly or to any venter. 2. Denoting a position more toward the belly surface than some other object of reference; same as anterior in human anatomy. [EU]

Ventricle: One of the two pumping chambers of the heart. The right ventricle receives oxygen-poor blood from the right atrium and pumps it to the lungs through the pulmonary artery. The left ventricle receives oxygen-rich blood from the left atrium and pumps it to the body through the aorta. [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]

Vinca Alkaloids: A class of alkaloids from the genus of apocyanaceous woody herbs including periwinkles. They are some of the most useful antineoplastic agents. [NIH]

Vincristine: An anticancer drug that belongs to the family of plant drugs called vinca alkaloids. [NIH]

Viral: Pertaining to, caused by, or of the nature of virus. [EU]

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]

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]

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]

Wound Healing: Restoration of integrity to traumatized tissue. [NIH]

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]

X-ray therapy: The use of high-energy radiation from x-rays to kill cancer cells and shrink tumors. Radiation may come from a machine outside the body (external-beam radiation therapy) or from materials called radioisotopes. Radioisotopes produce radiation and can be placed in or near the tumor or in the area near cancer cells. This type of radiation treatment

is called internal radiation therapy, implant radiation, interstitial radiation, or brachytherapy. Systemic radiation therapy uses a radioactive substance, such as a radiolabeled monoclonal antibody, that circulates throughout the body. X-ray therapy is also called radiation therapy, radiotherapy, and irradiation. [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]

Zebrafish: A species of North American fishes of the family Cyprinidae. They are used in embryological studies and to study the effects of certain chemicals on development. [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]

INDEX

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