Congressionally Directed Medical Research Programs

History: The Congressionally Directed Medical Research Programs (CDMRP) was born from a powerful grassroots effort led by the breast cancer advocacy community, which convinced Congress to appropriate funds for breast cancer research. This enabled a unique partnership among the public, Congress, and military. The CDMRP was created within the U.S. Army Medical Research and Materiel Command in fiscal year 1993 (FY93) to manage these funds. The CDMRP has grown to encompass multiple targeted programs and has received over $3 billion in appropriations from its inception in FY93 through FY05. Funds for the CDMRP are added to the Department of Defense budget where support for individual programs like the Chronic Myelogenous Leukemia Research Program is allocated via specific guidance from Congress.

U.S. Army Medical Research and Materiel Command

Proposal Review Process: The CDMRP uses a two-tier review process for proposal evaluation. Both steps in this process involve dynamic interactions between scientist reviewers and non-scientific consumer reviewers. Scientific reviewers and other professionals are selected for their subject matter expertise. Consumer reviewers provide a perspective that is complementary to the scientific expertise. The first tier of evaluation is a scientific peer review of proposals against established criteria for determining scientific merit. The second tier is a programmatic review of proposals, conducted by the Integration Panel (IP) (composed of scientists, clinicians, and consumers), that compares submissions to each other and recommends proposals for funding based on scientific merit, portfolio balance, and overall goals of the program.

Approximately 200 world-renowned scientists, clinicians, policymakers, and consumer advocates have served on the CDMRP's Integration Panels.

More than 3,000 scientists, clinicians, consumer advocates, and other professionals have brought their expertise to scientific peer and programmatic review.

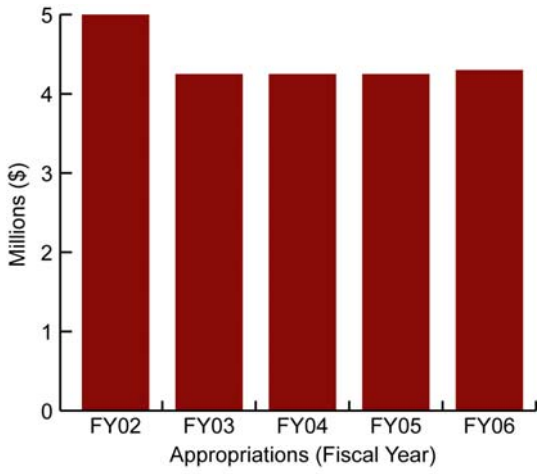
Almost 7,000 scientists and clinicians have received awards from the CDMRP.

More than 90 scientists, clinicians, and professionals manage the CDMRP.

The Chronic Myelogenous Leukemia Research Program (CMLRP)

Vision: The goals of the CMLRP are to improve the (1) understanding of the pathophysiology of chronic myelogenous leukemia (CML), (2) diagnosis of CML, (3) treatment of CML, and (4) quality of life for individuals living with CML and their families.

History: The CMLRP was established in FY02 to promote innovative research focused on eliminating CML. Appropriations for the CMLRP from FY02 to FY06 totaled $22.05 million.



Award Mechanisms: One goal of the CMLRP is to offer award mechanisms that fill important funding gaps within the research funding community. Because of the flexible and adaptive nature of the vision setting process, the CMLRP can be responsive to the needs of the research community by offering targeted award mechanisms. Award mechanisms offered by the CMLRP have ranged from the small, highly innovative, high-risk Exploration-Hypothesis Development Award designed to support studies that will lead to the formation of a viable hypothesis, to the larger, product-oriented Therapeutic Development Award designed to support the development of new treatment agents for CML. A total of 45 awards were made from FY02 through FY05.

Consumer Advocate Participation: As active members of the CMLRP, consumer advocates participate in setting program priorities and making funding decisions. Seven consumer advocates have served on CMLRP peer and programmatic review panels since 2002. Consumer advocates' firsthand experience with CML provides a unique perspective that is complementary to the scientific expertise of the panels. This perspective helps the scientist understand the human side of how research will impact the community and allows for funding decisions that reflect the concerns and needs of patients, the clinicians who treat them, and survivors and their families. An additional benefit is that consumer advocates take what they have learned back to their communities. This results in increased awareness of the importance of research and a stronger relationship between the scientific community and the consumer advocate community. The overwhelming success of the CDMRP precedent for including consumer advocates in the review process has influenced other funding agencies to follow suit.

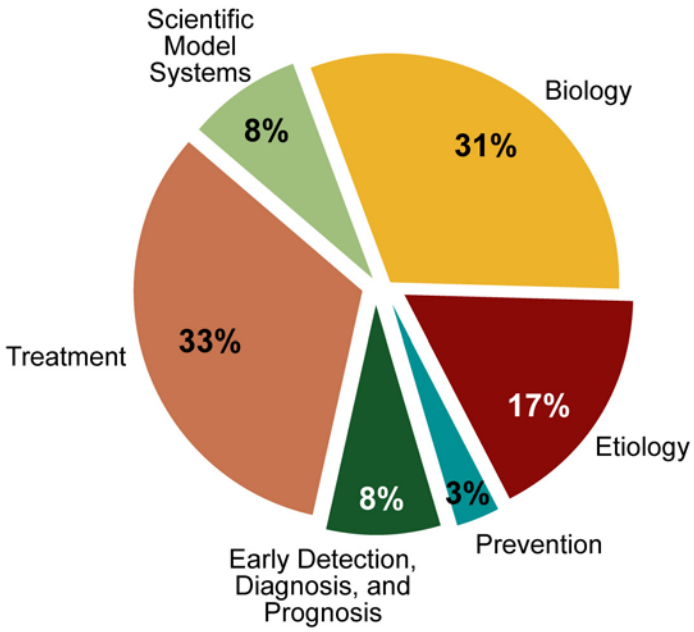
The intelligence and commitment of everyone on the [peer review] panel - all extremely dedicated to finding a cure - has convinced me that there will soon be a cure for CML.

Mr. David Cranmer, CMLRP Peer Review participant

Scientific Innovation: Innovation is a significant feature of many award mechanisms offered by the CMLRP. Proposed research deemed innovative may represent a new paradigm, challenge existing paradigms, or look at existing problems from new perspectives or using new technologies.

Disease Impact: The potential impact of proposed research (either in the near or more distant future) on the health and welfare of individuals living with CML is taken into account during both tiers of the proposal review process. High-impact research may significantly advance current methods, concepts, prevention, diagnosis, or treatment of CML or quality of life for patients.

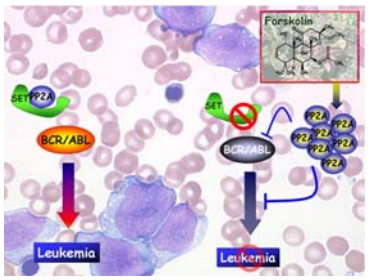
CMLRP-Funded Research Portfolio: During programmatic review, the IP seeks to fund a balanced portfolio of scientifically meritorious research. To achieve this balance, the IP needs to have the program portfolio analyzed using a categorization scheme. Studies funded by the CMLRP have been categorized through the Common Scientific Outline (CSO), a classification system originally developed jointly by the CDMRP and the U.S. National Cancer Institute. The CSO is now directed and managed by the International Cancer Research Partners (ICRP), a group of 7 U.S. cancer funding organizations including the CDMRP and 18 member organizations under the umbrella of the National Cancer Research Institute of the U.K. The ICRP members work to strategically coordinate cancer research funding by using the CSO to categorize their research portfolios across 7 broad areas of science. CMLRP-funded research falls into the following CSO categories: early detection, diagnosis, and prognosis; treatment; scientific models systems; biology; etiology; and prevention.



CMLRP Research Highlights

Unraveling Disease Progression

Danilo Perrotti, M.D., Ph.D., The Ohio State University



Underlying mechanisms of CML progression from the chronic phase to the blast crisis stage are not well understood and probably involve changes in a range of cellular and molecular processes. Changes in the regulation of mRNA metabolism may correlate with CML progression. Dr. Danilo Perrotti designed a research program focused on evaluating the effects of the BCR/ABL protein, the oncogenic tyrosine kinase responsible for leukemic transformation, on mRNA metabolism. Ribonomics was used to identify mRNAs that may contribute to the blast crisis CML cell phenotype. The Ribonomics screen demonstrated that RNA-binding proteins expressed in BCR/ABL-positive CML cells were associated with the mRNA of the protein phosphatase 2A (PP2A) and with the RNA of the inhibitor of PP2A (SET), suggesting that expression and function of PP2A might be regulated during transition of CML into blast crisis. PP2A is an important regulator of cell proliferation, survival, and differentiation, and it has been recently described as a tumor suppressor whose activity is altered in many types of cancer. Dr. Perrotti found that PP2A function is progressively lost in CML patients who progress into blast crisis through the inhibitory activity of SET, an inhibitor of PP2A that is induced by BCR/ABL activity. Blocking BCR/ABL activity with imatinib mesylate reestablished PP2A activity. Dr. Perrotti and his colleagues demonstrated increased expression of active PP2A through molecular or pharmacologic means leads to inactivation of regulators that are important for the proliferation and survival of CML progenitor cells suggesting that new CML treatments may be possible through the development of therapeutics aimed at upregulating PP2A activity in BCR/ABL-positive CML.

- Publication: Neviani P, Santhana R, Trotta R, et al. 2005. *Cancer Cell* 8:355–368

Development of CML Models

A. Thomas Look, Ph.D., Dana-Farber Cancer Institute, Kevin J.P. Griffin, Ph.D., University of California, Los Angeles

The common home aquarium zebrafish, *Danio rerio*, has moved from "pet status" to become an important whole organism model added to the repertoire of tools used for gene expression and protein activity studies. Whole organism studies are invaluable for asking more encompassing biological questions and when combined with data obtained from in vitro studies the resulting knowledge can lead to powerful insights into the specific mechanisms and the general consequences of disease. Developmental and biological conservation between zebrafish and mammals is evident down to the level of gene expression and function. Zebrafish are an interesting and excellent genetic model for studying human disease initiation and progression because of their biological and genetic complexity and they have been used as model organisms for studies of many human diseases including cancers such as leukemia. The strong conservation of sequence, expression, and function of key hematopoietic genes and proteins between zebrafish and mammals suggests that zebrafish may be a superior model for the investigating CML disease initiation and progression and potential therapeutic intervention. The CMLRP has funded two independent research proposals focused on creating transgenic zebrafish models of human CML through the myeloid-specific expression of the BCR/ABL protein that is implicated in the development of disease. One study will evaluate effects of BCR/ABL on proliferation and survival of myeloid cells, and another study will look at secondary mutation events that lead to the genesis of CML. Studies using these little fish may lead to a significant increase in the understanding of CML development and progression.

Potential Combinatorial Therapy for CML

Steven Grant, M.D., Virginia Commonwealth University

Imatinib mesylate (Gleevec) has had a major impact on the treatment of CML, a type of cancer in which the bone marrow makes too many white blood cells. Imatinib mesylate works by blocking an abnormal version of the BCR/ABL fusion protein found in 95% of the leukemia cells of CML patients. This abnormal protein probably causes the disease to develop. However, imatinib mesylate does not work in as many as 20% of CML patients. These patients have changes in their BCR/ABL protein that the drug cannot recognize. Scientists are trying to stop some of the important changes that lead to the growth and spread of cancer cells that do not respond to imatinib mesylate. Dr. Steven Grant of Virginia Commonwealth University is investigating several agents that may slow the changes that cause cells to become cancer cells and stop the cancer cells from spreading. These agents include histone deacetylase inhibitors (HDACIs), bortezomib, and flavopiridol. The effect of these agents, alone or in combination, leads to cell death. Dr. Grant found that using a combination of HDACIs and bortezomib or a combination of bortezomib and flavopiridol leads to the death of CML cells that have the BCR/ABL protein, including cells that do not respond to imatinib mesylate. Both treatment combinations damaged the cancer cells, which led to their self-destruction. The combination of bortezomib and flavopiridol also reduced the production of BCR/ABL protein and decreased the levels of BCR/ABL. Dr. Grant is working to discover how these combinations of agents work. He is studying CML cells from patients whose cancer responds to imatinib mesylate and from patients whose cancer is not affected by the drug. These studies may lead to new combinations of drugs to treat imatinib mesylate-resistant CML.

Preclinical Evaluation of a CML Therapeutic Agent

Robert L. Ilaria Jr., M.D., University of Texas Southwestern Medical Center

Most CML develops because a genetic event results in the expression of a fusion protein, BCR/ABL. Imatinib mesylate (Gleevec®) has been used to treat CML patients successfully in the early stages of disease. However, imatinib mesylate treatment of patients in the later stages of CML has not been as successful, and there is evidence of imatinib mesylate-resistant CML. Development of alternative treatment options such as the compound PD166326 might benefit CML patients. Dr. Robert L. Ilaria Jr. studied PD166326, a promising potential CML therapeutic agent, in a preclinical mouse model of human CML. Data generated from this research was the first to move studies of PD166326 from the in vitro setting to the in vivo setting, a critical first step to bring this agent to human clinical trials. Using this mouse model of CML, Dr. Ilaria and colleagues demonstrated that PD166326 quickly reached therapeutic levels in the blood stream and was well tolerated by the mice. More importantly, PD166326 suppressed leukemic cell growth and was useful in treating a mouse model of imatinib-resistant CML. PD166326 treatment in mice that have a CML-like myeloproliferative disorder reduced leukemic cells better than treatment with imatinib mesylate. Additionally, splenomegaly, a characteristic of this CML-like myeloproliferative disorder, in PD166326-treated mice was reduced along with peripheral blood granulocytosis when compared to imatinib mesylate- or placebo-treated mice. PD166326 also suppressed other intracellular events that may be involved in the development of cancer cells. Taken together, these data suggest that PD166326 may be an effective addition to the arsenal of CML treatment options.

- Publication: Wolff NC, Veach DR, Tong WP, et al. 2005. *Blood* 105:3995–4003.

http://cdmrp.army.mil/cmlrp