Chronic Myelogenous Leukemia Research Program

History

The Department of Defense Chronic Myelogenous Leukemia Research Program (CMLRP) was established in fiscal year 2002 (FY02) by the Joint Appropriations Conference Committee Report No. 107-350, which provided $5 million (M) for CML. The Congressionally Directed Medical Research Programs (CDMRP) was established within the U.S. Army Medical Research and Materiel Command to manage programs such as the CMLRP that were created in response to the concerns of those directly affected by the disease and that were specified by Congress.

After receipt of the FY02 appropriation for CML, a stakeholders' meeting was held in April 2002 to obtain input from scientific and consumer stakeholders on major issues in CML research. For the CMLRP, consumers are patients, survivors, or family members of those living with CML. Following the stakeholders' meeting, the program's first Integration Panel (IP), a panel of scientists, clinicians, and consumers with expertise in CML, was configured to recommend the FY02 vision and investment strategy. The overall goal of the CMLRP was to support research leading to substantial improvement in the understanding, diagnosis, and treatment of CML and enhance the quality of life of persons with the disease.

Congress appropriated additional funds to the CMLRP in subsequent years, totaling $22.05M through FY06. The CMLRP has supported 61 awards across four mechanisms: the Investigator-Initiated Research, Hypothesis Development, New Investigator, and Therapeutic Development Awards. Research awards were made using a two-tier review process composed of peer and programmatic reviews that ensures scientific merit and attainment of program goals. Additional information about the CDMRP and the two-tier review system can be accessed at http://cdmrp.army.mil/.

Program Outcomes

The outcomes of CMLRP-funded research can be gauged in part by the number of resultant publications (128), abstracts/presentations (166), and patents (14) reported by awardees to date. Projects funded by this program span basic, clinical, and population-based research. Details on each award funded are located on the CDMRP website under Search Awards at http://cdmrp.army.mil.

Vision

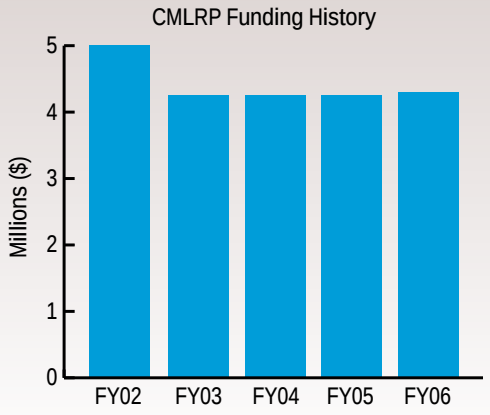
To eradicate chronic myelogenous leukemia (CML).

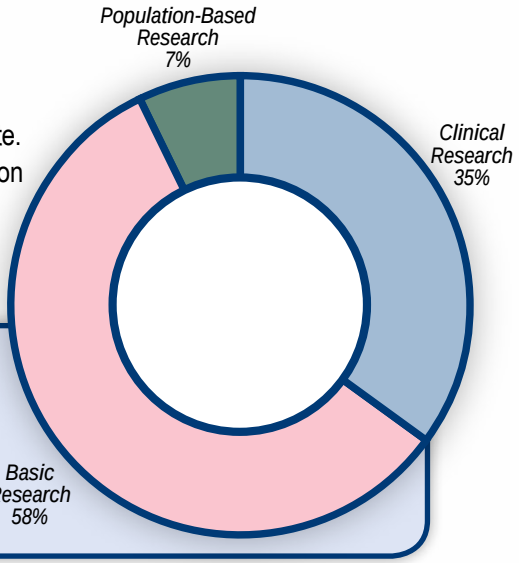
Mission

To identify and sponsor basic and clinical research in the field of CML.

Goals

To improve the (1) funding of high-risk, high-impact research not supported by other mechanisms, (2) understanding of the basic science of CML, (3) treatment of CML, and (4) quality of life of individuals with CML.





FY02–FY06 CMLRP Portfolio by Research Area

Population-Based Research (7%)
- Research Resources (7%)

Clinical Research (35%)
- Clinical and Experimental Therapeutics (33%)
- Detection and Diagnosis (2%)

Basic Research (58%)
- Cell Biology (22%)
- Genetics and Molecular Biology (20%)
- Pathobiology (9%)
- Immunology (7%)

CMLRP-Supported Initiatives

Attacking Gleevec-Resistant CML Cells

Imatinib (Gleevec, ST1571) has been successfully used for the treatment of Philadelphia chromosome-positive CML. This drug was designed to inhibit an oncogenic tyrosine kinase (BCR-ABL) that is present in nearly all CML patients. By blocking BCR-ABL, imatinib kills the leukemic cells. However, following chronic treatment with imatinib, a subset of patients develops resistance to the drug through the development of mutations that prevent the binding of imatinib to BCR-ABL. Thus, it has become important to develop novel inhibitors that are active against imatinib-resistant mutants of BCR-ABL. Dr. E. Premkumar Reddy of Temple University was funded by the CMLRP to develop alternative compounds that inhibit BCR-ABL. By employing high-throughput screening, Dr. Reddy and colleagues identified novel small molecule inhibitors of BCR-ABL that inhibit the growth and induce apoptosis of imatinib-resistant tumor cells. One of these compounds, ON044580, was selected for further investigation and is currently undergoing preclinical evaluation in preparation for Phase I human trials. Interestingly, this compound also inhibits the kinase activity of another oncogenic tyrosine kinase, JAK2, which has recently been shown to be mutated in several myeloproliferative diseases that do not contain a BCR-ABL translocation. It is therefore possible that this compound could have multiple therapeutic applications including Gleevec-resistant CML and myeloproliferative neoplasms that harbor JAK2 mutations.

FTY720 - A New Alternative for Treating CML

Unbalanced activity of cellular kinases and phosphatases is often associated with tumor development and progression. Almost all CML patients carry the Philadelphia chromosomal translocation t(9;22)(q34:q11) that creates the oncogene BCR-ABL. Dr. Danilo Perrotti, a CMLRP-funded investigator, previously reported that the phosphatase activity of the tumor suppressor protein phosphatase 2a (PP2A) is functionally inactivated in blast crisis CML through the inhibitory activity of a BCR-ABL-regulated protein. With funding from the CMLRP, Dr. Perrotti further investigated whether suppression of PP2A contributes to the progression of CML and whether activation of this phosphatase prevents disease progression.
Dr. Perrotti and colleagues showed that the PP2A activator FTY720 (also known as fingolimod) efficiently antagonizes disease progression, inhibits self-renewal, and induces apoptosis in CML patient cells. They also demonstrated that long-term administration of FTY720 in mice does not induce adverse effects. Thus, Dr. Perrotti's research underscores the therapeutic relevance of PP2A activators such as FTY720 in the treatment and possible eradication of CML.

Animal Models of CML

Appropriate animal models of human disease are valuable tools used in understanding disease initiation and progression as well as the development of effective therapeutic agents. One of the challenges for animal model development is the creation of models that mimic human disease or respond to therapy in a manner that translates to the clinic. The CMLRP funded the establishment of both mouse and zebrafish models of CML to better study the disease. For example, Dr. Ricardo Feldman of the University of Maryland combined the advantages of tissue-specific transgenic technology with the flexibility of retroviral-mediated gene transfer to create a new mouse model of CML with hematopoietic-specific expression that more accurately reflects the etiology and progression of the human disease. Dr. Kevin Griffin of the University of California, Los Angeles generated a zebrafish model of CML that expresses the human BCR-ABL enzyme. These fish are being used to identify genetic mutations involved in the development of leukemia as well as to evaluate potential new treatment agents.