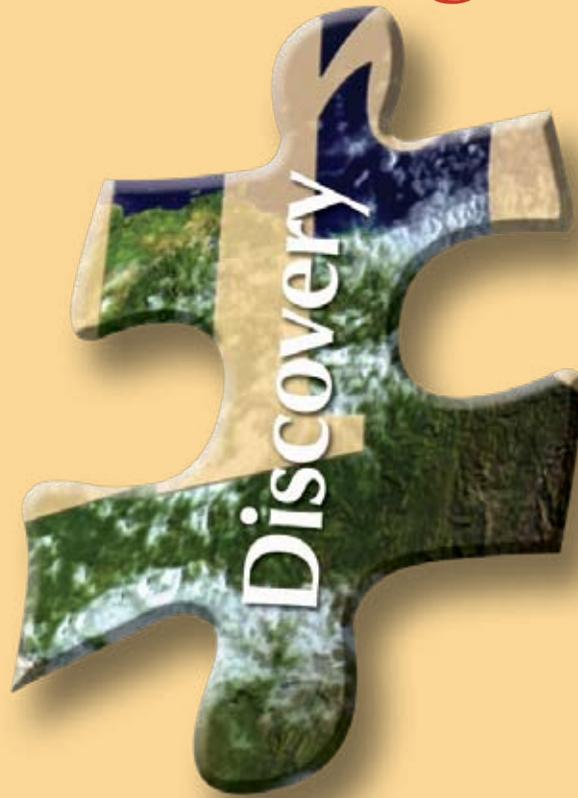


CONGRESSIONALLY DIRECTED
MEDICAL RESEARCH PROGRAMS:
PARTNERING FOR A CURE

VII. Chronic Myelogenous Leukemia Research Program





Vision

To perfect the existing and develop new diagnostic and therapeutic approaches for chronic myelogenous leukemia.

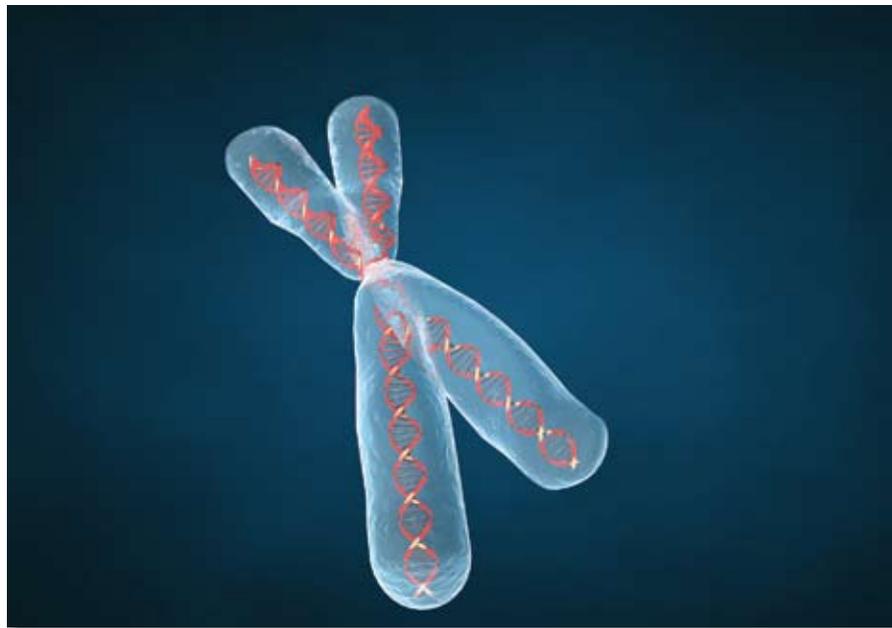
Mission

To sponsor basic and clinically oriented research in the field of chronic myelogenous leukemia.



The Disease

Chronic myelogenous leukemia (CML), also known as chronic granulocytic leukemia or chronic myeloid leukemia, is an overgrowth of granulocytes, a type of white blood cell. 🌟 In 2006, approximately **4,500** individuals will be diagnosed with CML, and an estimated **900** will die from the disease.¹ 🌟 The cause of this disease is unknown. 🌟 In most cases, CML is characterized by a chromosomal abnormality that is known as the Philadelphia chromosome.



¹ National Cancer Institute Physician Data Query and American Cancer Society, Cancer Facts and Figures, 2006.



Signs and Symptoms

CML is divided into three phases called chronic, accelerated, and acute depending on the stage of the leukemic cells. Symptoms of CML usually develop gradually over time.

- ❖ In the early or chronic stage of CML, there are usually few to no symptoms of leukemia detectable. However, as CML progresses, nonspecific symptoms may become noticeable.
- ❖ Indicators of the accelerated phase include signs such as weakness, fatigue, fever, poor appetite, weight loss, increased sweating, and an enlarged spleen.
- ❖ The acute phase, also called the blast phase, is characterized by significant symptoms that may include weight loss, anemia, fever, bone pain, and recurring infections.



Program Background

The Department of Defense (DOD) Chronic Myelogenous Leukemia Research Program (CMLRP) was established in fiscal year 2002 (FY02) by Joint Appropriations Conference Committee Report No. 107-350, which provided \$5 million (M) for CML research. The CMLRP has managed \$22.05M through FY06 to fund peer-reviewed research, and 47 awards have been funded through FY05 to improve the diagnostic and therapeutic approaches to CML (see Figure VII-1 – CMLRP History). Whether supporting basic and clinically oriented research, encouraging highly innovative research, or sponsoring the development of potential CML-specific therapeutic agents, the CMLRP is exploring new frontiers in the field of CML research. Today, as the CMLRP celebrates its fifth anniversary, the program truly is impacting the health and welfare of individuals living with CML.

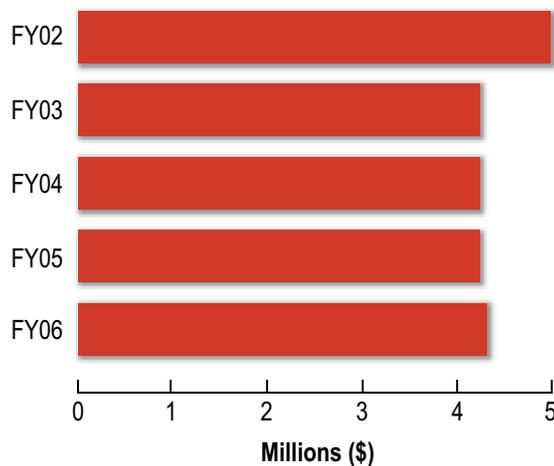


Figure VII-1. CMLRP History



The Program Today

Fiscal Year 2005 Summary

The CMLRP was continued through an FY05 congressional appropriation of \$4.25M. The emphasis for the FY05 program was placed on therapeutics and innovation. Two award mechanisms were offered, the Therapeutic Development Award and the Exploration–Hypothesis Development Award. A total of 54 proposals were received, as detailed in Table VII-1, and 11

awards were made. As illustrated in Figure VII-2, the FY05 CMLRP has supported a multidisciplinary portfolio of research.

2005 Fiscal Year
54 Proposals Received
\$4.25M in Appropriations
11 Awards

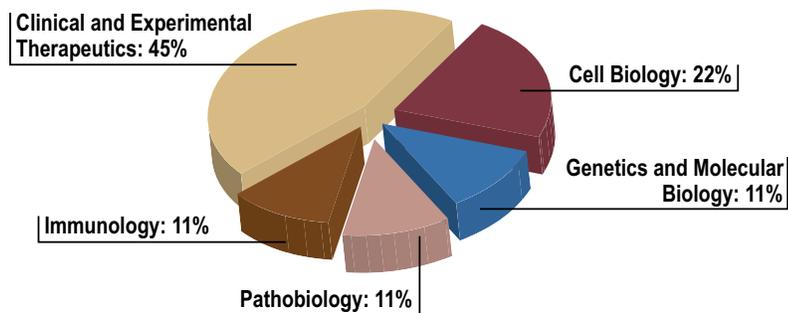


Figure VII-2. FY05 CMLRP Portfolio by Research Area

Table VII-1. Funding Summary for the FY05 CMLRP

Categories and Award Mechanisms	Proposals Received	Awards	Investment
Research			
Exploration–Hypothesis Development	45	10	\$1,620,722
Therapeutic Development	9	1	\$2,000,526
TOTAL	54	11	\$3,621,248

Fiscal Year 2006 Summary

Congress appropriated \$4.3M to the CMLRP in FY06. Two award mechanisms offered in FY06 emphasized innovation. Exploration–Hypothesis Development Awards will support untested, groundbreaking concepts in CML research while New Investigator Awards will support discoveries in clinical translational research. A total of 63 proposals were received, as shown in Figure VII-3, and approximately 14 awards are anticipated. Appendix B, Table B-6, summarizes the congressional appropriations and investment strategy executed by the CMLRP for FY05 through FY06.

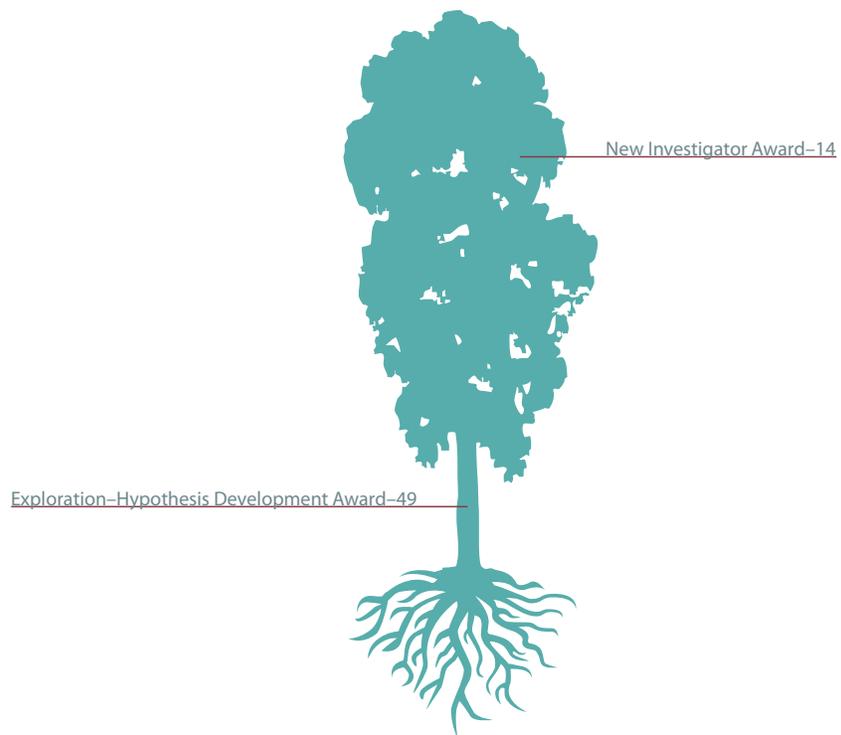
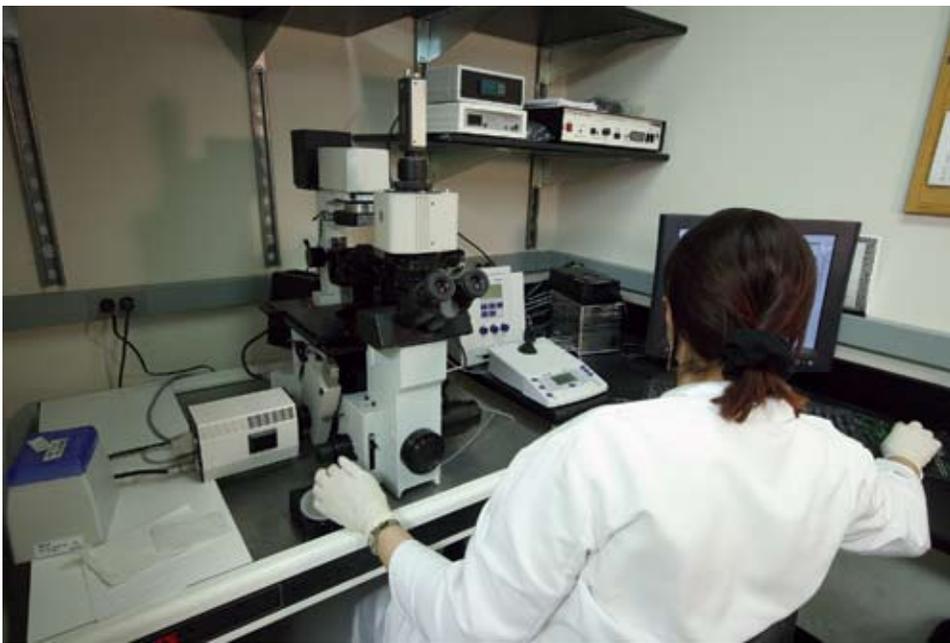


Figure VII-3. Award Mechanisms Offered and Proposals Received for the FY06 CMLRP



Recognizing Outstanding People

Exceptional people—scientists, research managers, and consumer advocates—are exploring new therapeutics for CML and uncovering the mysteries of CML development and progression. The program recognizes the passion and vision of all of those involved in making this effort a success.



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 experiences with CML provide 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. As a result, there is an increased awareness of the importance of research and a stronger relationship between the scientific and the consumer advocacy communities. More information about consumer involvement can be found in Chapter I.

MR. KELVIN DICKENSON, FY06 CMLRP INTEGRATION PANEL MEMBER

"I feel very blessed to have survived CML and now have the chance to contribute to processes that will lead to a cure." Kelvin Dickenson has been cancer-free for 5 years and credits the disease with allowing him the opportunity to meet many special people whom he may not have met otherwise. Since being diagnosed with CML, Kelvin has spent many hours becoming "medically educated" and has realized the importance



of health, fitness, and nutrition in daily life. He volunteers in the Leukemia and Lymphoma Society's First Connection Program, a peer-to-peer program that pairs newly diagnosed patients and their caregivers with a more experienced patient who can lend thoughtful, knowledgeable support. A risk management consultant for Dun and Bradstreet, Kelvin is a devoted father who loves to spend time with his two boys. He is an avid photographer and enjoys tae kwon do. A member of the FY06 CMLRP Integration Panel (IP), Kelvin initially was introduced to the program through his volunteer work with the Leukemia and Lymphoma Society. Kelvin served as a member of the CMLRP peer review panel in both FY03 and FY04.

Prior to joining the IP, he served as an ad hoc reviewer for the CMLRP programmatic review in FY05. Kelvin characterizes his time with the CMLRP as truly amazing. "I have been exposed to a wide number of truly talented researchers and clinicians and witnessed a tremendous commitment to finding cures." The CMLRP is inspired by the dedication and courage of people like Kelvin Dickenson, who overcame hardships to make a positive difference in the lives of others.



Scientific Community

The scientific community has and will continue to be a driving force in the cure for CML. To date, 44 researchers in the CML community have been funded by the CMLRP.

KRZYSZTOF W. PANKIEWICZ, PH.D., PEER REVIEW PANEL MEMBER

Dr. Krzysztof Pankiewicz is an Associate Director and Professor at the University of Minnesota Center for Drug Design in Minneapolis, Minnesota. "It is a privilege and honor to serve as a member of the peer review panel of the CMLRP administered by the DOD. During the past 2 years, we reviewed more than 120 grant applications proposing new approaches for treatment of CML. New targets and new drug candidates were discovered or are under development, which brings hope that this disease will be suppressed to a previously unimaginable level. The first magic bullet against CML, imatinib, soon will be supported or replaced by new, even more specific and effective drugs. All members of the process, the Principal Investigators, scientific and particularly consumer reviewers, as well as the meeting organizer...did an excellent job. I had a feeling that all forces (Army, Marines, Navy, and Air Force) were in place to help fight CML."



KATHLEEN SAKAMOTO, M.D., PEER REVIEW PANEL MEMBER

Dr. Kathleen Sakamoto is a Pediatric Hematologist-Oncologist at the Mattel Children's Hospital at the University of California, Los Angeles. "The CDMRP is providing an opportunity to do cutting-edge research that would otherwise not be funded to identify new ways of treating CML."

MARIA TERESA RIZZO, M.D., PEER REVIEW PANEL MEMBER

Dr. Maria Teresa Rizzo is an Associate Investigator in the Signal Transduction Laboratory at the Methodist Research Institute, Clarian Health Partners in Indianapolis, Indiana. "My experience on the CML review panel was very positive for several reasons. I felt that [it] was a privilege and honor to have been asked to provide my scientific expertise in the evaluation of the proposals... Most of all, I felt enriched at a personal level by the presence of the consumer reviewers."



Integration Panel Members

The CMLRP IP is composed of eminent research scientists, clinicians, and consumer advocates that are all leaders in their respective communities. The IP refines the program focus and investment strategy, assists in policy development, and recommends a broad portfolio of grants for funding that reflects the investment strategy for that particular program cycle (for more information about the functions of the IP see Chapter I). Thus, the active input of the IP helps enable the CMLRP to find and fund the best research and set important program priorities aimed at developing new diagnostic and therapeutic approaches for CML.

FY06 CMLRP IP Members

JERALD P. RADICH, M.D. (CHAIR), FRED HUTCHINSON CANCER RESEARCH CENTER

RICHARD A. VAN ETTEN, M.D., PH.D. (CHAIR EMERITUS), TUFTS-NEW ENGLAND MEDICAL CENTER

RAVI BAHTIA, M.D., CITY OF HOPE NATIONAL MEDICAL CENTER

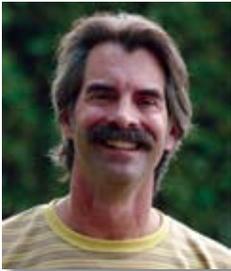
LOUIS J. DEGENNARO, PH.D., THE LEUKEMIA AND LYMPHOMA SOCIETY

KELVIN J. DICKENSON, THE LEUKEMIA AND LYMPHOMA SOCIETY

ALAN J. KINNIBURGH, PH.D., NATIONAL HEMOPHILIA FOUNDATION

GWEN NICHOLS, M.D., COLUMBIA UNIVERSITY MEDICAL CENTER





JERALD P. RADICH, M.D., FY06 CMLRP INTEGRATION PANEL CHAIR

Dr. Jerald Radich, Professor in the Clinical Research Division Program in Genetics and Genomics at the Fred Hutchinson Cancer Research Center in Seattle, Washington, served as the FY06 IP Chair. “This is a challenging time for medical research. On one hand, advances in basic biology, computational biology, and technology allow investigators to ask questions never before considered. On the other hand, world events have conspired to make funding dollars exceedingly tight, making it an especially tough road for young investigators and those with particularly novel, high-risk ideas. The Army’s CDMRP fills an essential gap, providing funding to novel and innovative research by both established and young investigators. Peer review by top scientists ensures the quality of the proposals, which ultimately provides productivity and advances. The CDMRP is a positive example of government programs helping citizens.”

ALAN J. KINNIBURGH, PH.D., CMLRP INTEGRATION PANEL MEMBER

Dr. Alan Kinniburgh, CEO of the National Hemophilia Foundation, was among the original group of distinguished scientists and consumer advocates who met at the CMLRP Stakeholders Meeting to identify the major issues facing CML research and develop an investment strategy for the CMLRP. “Since FY02, the DOD CMLRP has made significant investments in research to fully understand CML—chronic phase, accelerated disease, and blastic crisis. It has funded new ideas, new model systems, and the development of new molecularly targeted drugs. As a member of the IP, I have had the privilege to participate in a process that may one day lead to new medicines



and even a possible cure for CML.”

Exploring New Therapies for CML

Treatment for CML usually consists of various chemotherapeutic agents used to disrupt the production of leukemic cells. These treatments may be followed by stem cell transplant. More recently, targeted therapy for CML with STI571 (Gleevec®), an Abl-specific tyrosine kinase inhibitor, has shown significant success in patients with advanced disease. However, resistance to this therapy has been observed, indicating that research is needed still. The CMLRP is meeting this need by sponsoring research that will advance the discovery of potential new CML-specific therapies.

COMBINATIONS OF NOVEL HISTONE DEACETYLASE AND BCR-ABL INHIBITORS IN THE THERAPY OF IMATINIB MESYLATE-SENSITIVE AND -REFRACTORY, BCR-ABL-EXPRESSING LEUKEMIA

The Bcr-Abl tyrosine kinase, a key factor in the development of CML, is a protein that can have a dramatic effect on the growth and survival of CML cells in the body. In non-CML cells, Bcr-Abl is not expressed. However, in CML, the unchecked activity of Bcr-Abl results in leukemic transformation of cells. For this reason, Bcr-Abl is an important therapeutic target in the treatment of CML, as exemplified through the use of imatinib mesylate (Gleevec). By targeting the deregulated Bcr-Abl tyrosine kinase, Gleevec is highly active in inducing clinical and cytogenetic remission. However, studies of patients who relapse demonstrate that after a median of 42 months of treatment, approximately 16 percent of patients develop mutations, making them resistant to Gleevec.

Dr. Kapil Bhalla of the Medical College of Georgia Cancer Center is addressing this problem with funding from an FY04 Therapeutic Development Award. Dr. Bhalla hypothesizes that the use of histone deacetylase (HDAC) inhibitors in combination with Bcr-Abl inhibitors, such as Gleevec, may circumvent resistance-associated mutations. HDAC inhibitors function to remove the acetyl group chemical modification from proteins; the addition or removal of this group can change a protein's behavior. Previously, Dr. Bhalla found that inhibition of HDAC-6 led to an increase in the acetylated form of heat shock protein 90 (hsp90). This acetylation inhibits the normal chaperone function of hsp90, which typically maintains the proper function and activity of a number of proteins in the cell. Among those proteins chaperoned by hsp90 is Bcr-Abl. Dr. Bhalla now has found that the loss of hsp90 function following treatment with HDAC-6 inhibitors leads to depletion of Bcr-Abl in both Gleevec-sensitive and -resistant primary CML cells, causing cell death. Furthermore, by combining the HDAC inhibitor with nilotinib or dasatinib, both potent next-generation Bcr-Abl inhibitors, an additive effect was found whereby Gleevec-resistant, blast-crisis cells were reduced to a greater extent than with either treatment alone. This is a promising new approach to treatment that may overcome resistance by targeting Bcr-Abl from several directions.



ATTACKING GLEEVEC-RESISTANT CML CELLS



With increased knowledge of the basic biology of aberrant, disease-causing cells found in the body, therapeutics now are being designed to target these cells specifically while sparing normal cells. This holds true for CML. Through the identification of a mutation in more than 90 percent of patients with CML that causes a mutated, constitutively active Bcr-Abl protein, researchers began focusing on inhibiting this protein. As a result, Gleevec was created. This compound blocks the activity of Bcr-Abl by binding to the kinase domain of the protein, which is responsible for its activity in causing CML. However, following chronic treatment with Gleevec, approximately 14 percent of patients develop a resistance to the drug through the development of mutations that prevent the binding of Gleevec to Bcr-Abl. For this reason, researchers have been examining the Bcr-Abl molecule to find other ways to inhibit its activity. Dr. E. Premkumar Reddy of Temple University has identified several compounds that target a different area or conformation of Bcr-Abl than Gleevec. Dr. Reddy believes that the region these compounds bind to is less likely to undergo mutation. It was found that these compounds inhibit Bcr-Abl specifically and kill Gleevec-resistant tumor cells by apoptosis. Through a DOD CMLRP FY05 Therapeutic Development Award, Dr. Reddy is conducting further studies with these compounds to determine their precise mechanism(s) of action, preclinical toxicology, and pharmacological properties with the goal of initiating one or more clinical trials for the treatment of patients with CML.



Exploring New Opportunities

Exploration of the underlying mechanisms of CML initiation and progression and the development of new therapeutic measures require a concerted effort by the scientific community. The CMLRP recognizes the importance of collaborative efforts and networking to achieve these goals. To facilitate the dissemination of research accomplishments, communication, and the development of future collaborations, the CMLRP will sponsor its first research conference in December 2006 called “Road to a Cure: The CMLRP Investigators Meeting.” The meeting will provide a means

for CMLRP-funded investigators and consumer advocates to share ideas, forge collaborations, and pursue promising new directions in CML research.



Road to a CURE

The Chronic
Myelogenous Leukemia
Research Program

Investigators Meeting

