CDMRP

Department of Defense

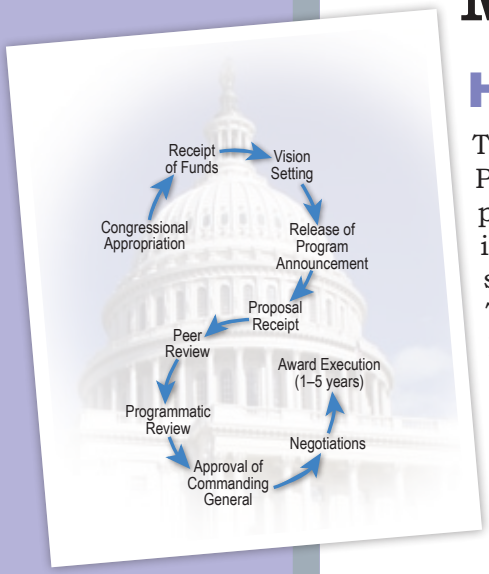
Peer Reviewed Cancer Research Program





U.S. Army Medical Research and Materiel Command

Congressionally Directed Medical Research Programs



History and Background

The Office of the Congressionally Directed Medical Research Programs (CDMRP) represents a unique partnership among the public, Congress, and the military. The vision of the CDMRP is to find and fund the best research to eradicate diseases and support the warfighter for the benefit of the American public. The CDMRP seeks to fill research funding gaps by focusing on high-risk, high-gain research with an emphasis on innovative ideas, breakthrough technologies, and novel partnerships. Since 1993, the CDMRP has grown to encompass multiple targeted programs. Although the programs within the CDMRP share many common features, each program is unique and emphasizes the specific needs of its research and advocacy communities. The CDMRP employs a flexible management cycle to maintain the individuality of each program while also meeting the needs of Congress, the DOD, the research and advocacy communities, and the public at large.

Key steps in the cycle are based on a two-tier review model recommended by the National Academy of Sciences' Institute of Medicine. The first tier is a peer review of proposals against established criteria for determining scientific and technical merit. Consumers participate equally with all other panel members in discussions and scoring of proposals at the scientific peer review process. The second tier is a programmatic review, conducted by the Integration Panel (an advisory board of leading scientists, clinicians, and consumers), that compares proposals against each other and recommends submissions for funding based on scientific merit, relative innovation and impact, portfolio balance, and overall program goals.

Consumers are individuals affected by the disease and represent the voice of their community. Working collaboratively with leading scientists and clinicians, consumers participate in setting program priorities, reviewing proposals, and recommending funding awards. The PRCRP consumers are survivors of melanoma and other skin cancers, colorectal cancer, kidney cancer, genetic cancers, and family members of those diagnosed with pediatric brain cancer.

"Involvement as a consumer advocate member on the Integration Panel of the PRCRP has given me a representative voice from the cancer community of patients, survivors, caregivers, and interested others. As a consumer advocate, I have been welcomed and viewed as an equal and valued partner by staff and by scientist members of this panel. My experience has been that the panel has consistently sought my input, listened carefully to it, and included it in the process."

Ron Whitten
Integration Panel
Consumer Member, FY09 – FY10

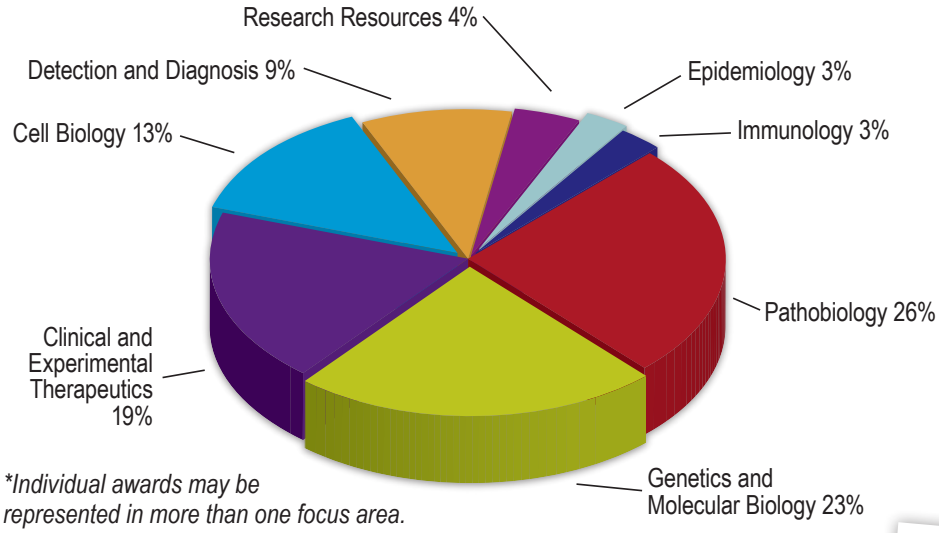
PRCRP Overview

The Peer Reviewed Cancer Research Program (PRCRP) was initiated by the U.S. Congress in fiscal year 2009 (FY09) with an appropriation of $16 million (M) for execution by the USAMRMC CDMRP. For FY10, the U.S. Congress directed $15M for the PRCRP for cancer research not addressed in the breast, prostate, lung, or ovarian cancer research programs currently executed by the CDMRP. Specific research topic areas for FY10 are melanoma and other skin cancers, pediatric brain tumors, genetic cancer research and genomic medicine, kidney cancer, blood cancers, colorectal cancers, *Listeria* vaccine for cancer, and radiation protection using nanotechnology. The PRCRP focuses on cancer research relevant to military beneficiaries.

Portfolio Analysis and Funding History

The PRCRP has offered award mechanisms to support a broad spectrum of research in the specified topic areas. For FY09, PRCRP supported four topic areas (melanoma and other skin cancer research, pediatric brain tumor research, genetic cancer research, and noninvasive cancer ablation treatment including selective targeting with nanoparticles), as directed by Congress, and funded research in a variety of research disciplines.

The PRCRP Portfolio Categorized by Research Disciplines*



**Individual awards may be represented in more than one focus area.*

"A deeper understanding of the immunobiology of melanoma and the multiple genetic pathways that drive this tumor and its immunosuppressive interactions with the immune system are critical to accelerate progress. The CDMRP is a welcome new avenue through which I hope we will make substantial progress against melanoma, genetic risks of cancer, pediatric brain tumors, and nanotechnology...."

John Kirkwood, M.D.
Integration Panel Member, FY09, and Integration Panel Chair, FY10

Congressional appropriations for the PRCRP:
FY09 – $16M
FY10 – $15M

Vision

To improve quality of life by decreasing the impact of cancer on service members, their families, and the American public

Mission

Foster groundbreaking and collaborative research to accelerate progress in cancer prevention, detection, and therapeutic interventions

"Serving on the Integration Panel for PRCRP has been a tremendous experience for me—one that I wish every cancer researcher could have. I have learned to look at things differently after listening to thoughtful comments made by cancer survivors and research advocates during our panel discussions. A real synergy of ideas developed as we talked about what the research objectives of the PRCRP should be for the coming year, to make a difference in the lives of people with cancer today while at the same time working to eradicate cancer for the generations to come."

Katherine Squibb, Ph.D.
Integration Panel Chair, FY09, and Integration Panel Chair Emeritus, FY10

Cancer Incidences in Military Beneficiaries

U.S. veterans, active duty service members, and their immediate families have been reported at higher risk and incidence for certain cancer types as compared to the U.S. general population. Overall, cancer illness has a significant impact on both the cost of the Military Health System, with over $1 billion spent in FY02, and on the warfighter's ability to complete the mission[1].

Malignancies Associated with Military Service

Exposure or Environmental Toxin	Associated Cancer
Full-body to nitrogen, sulfur mustard or nitrogen mustard[2]	Nasopharynx, larynx, lung (except mesothelioma), squamous cell carcinoma of the skin, and acute nonlymphocytic leukemia
Ionizing radiation[2, 3]	Leukemia (except chronic lymphocytic leukemia), thyroid, bone, brain, breast, colon, lung, ovary, pharynx, esophagus, stomach, small intestine, pancreas, bile ducts, gall bladder, salivary gland, urinary tract (kidneys, renal pelvis, ureter, urinary bladder and urethra), lymphomas (except Hodgkin's disease), multiple myeloma, primary liver cancer, and bronchioloalveolar carcinoma (a rare lung cancer)
Certain herbicide agents[2, 4, 5]	Non-Hodgkin's lymphoma, soft-tissue sarcoma (other than osteosarcoma, chondrosarcoma, Kaposi's sarcoma, or mesothelioma), Hodgkin's disease, multiple myeloma, respiratory cancers (lung, larynx, trachea, and bronchus), prostate cancer, chronic lymphocytic leukemia
Specific physical, chemical, or biological factors (electromagnetic fields, jet fuel, volatile organic materials, etc.)[2, 6, 7, 8]	Melanoma, testicular, thyroid, cervical, vulvar, oral squamous cell, pancreatic, and uterine

[1]Crawford RS et al. 2007 *Military Medicine* 172:1084-1088.
[2]Veterans Health Administration (VHA) Directive 2003-034, June 20, 2003.
[3]Zhu K et al. 2009. *Cancer Epidemiol Biomarkers Prev* 18:1740-1745.
[4]Frumklin H. 2003. *CA Cancer J Clin* 53:245-55.
[5]The Selected Cancers Cooperative Study Group. 1990. *Arch Intern Med* 150:2473-2483.
[6]Department of Defense Automated Central Tumor Registry,http://www.afip.org/consultation/actur/data00.htm.
[7]D'Este C et al. 2008 *Am J Ind Med* 51:16-23.
[8]Dalanger NA et al. 1995. *J Occup Environ Med* 37:298-305.

Developing Biomarkers and Diagnostic Platforms

Alan Cantor, M.D., Ph.D.,
Children's Hospital, Boston, Massachusetts

Searching for Novel Leukemia Predisposition Genes

Dr. Alan Cantor received an FY09 Idea Award to identify a novel set of genes and their mutations responsible for developing myelodysplastic syndrome and leukemia. Cbf-beta, GATA1/2, and Fli1, interacting partners of Runx-1, which is frequently mutated in sporadic human leukemias, have been selected as potential candidates for this study. Dr. Cantor will examine them for the presence of mutations utilizing DNA samples collected from patients and their family members. To determine whether the inherited allele is associated with disease, Dr. Cantor plans to employ a microsatellite markers flanking approach to scan the selected genetic loci. The linkage of the identified mutations to the disease and the function of the altered gene products will be determined following gene sequencing. To identify novel disease-linked genomic regions beyond just a few selected gene candidates, he also proposes to use high-density single nucleotide polymorphism arrays. Ultimately, this research project may lead to the development of the next generation of molecular-based risk assessment tools for leukemia and new preventive treatments to reduce the risk of developing radiation/chemical exposure-induced leukemia, which is especially relevant to Armed Forces members and their families.

Ying-Hsui Su, Ph.D.,
Drexel University, Philadelphia, Pennsylvania

Noninvasive Genetic Urine Test for Colon Cancer Screening

By exploiting the technique of padlock probe mediated amplification, Dr. Ying-Hsiu Su of Drexel University hopes to design a new method to detect colorectal cancer from collected urine. Human urine contains short (< 300 bp) fragmented DNA from different sources throughout the body. The padlock probe will utilize known cancer gene sequences to identify possible DNA from colorectal cancer. Funded by an FY09 Concept Award, Dr. Su and colleagues will screen the amplified products through DNA microarray analyses to identify any colorectal cancer-specific genes in the urine of patients. A fast, easy screening method for colorectal cancer would increase compliance for screening and earlier detection of colorectal cancer, thus leading to better outcomes.

"The people I have met and work alongside as a Consumer Reviewer for CDMRP, are among the smartest and most compassionate medical professionals I have ever met! And I have met many. I am proud to be a small part of this truly incredible group that has the well-being of the many, for many generations to come, at heart."

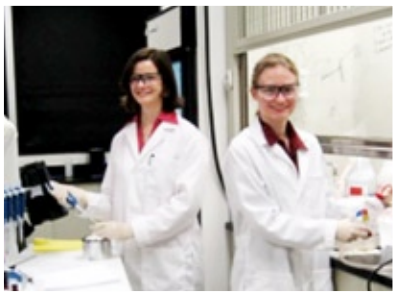
John F. Kennedy
Peer Review Consumer Reviewer, FY09

To fight esophageal cancer, Mr. Kennedy underwent a treatment with a powerful chemical, which made every cell in his body extremely photosensitive. The complete story is published on: http://cdmrp.army.mil/cwg/stories/2010/jkennedy_profile.shtml.

Andrea M. Armani, Ph.D., University of Southern California, Los Angeles, California

A Novel Laser-Based Method for DNA Methylation Detection

Dr. Andrea Armani, a recipient of a New Investigator Award in FY09, is developing a new sensing instrument that can be used to detect and characterize epigenetic markers for cancer. The first nanolaser transducer for biological sensing is designed to detect oligonucleotides and methylated DNA at the single molecule level. To accomplish this extremely challenging goal, she is collaborating with Dr. Mark Thompson from the University of Southern California (USC) Chemistry Department, and Dr. Peter Laird, Director of the USC Epigenome Center of the Keck Medical School. The development of this laser-based method has the potential to revolutionize current experimental design methods used by researchers in biology, chemistry, and clinical fields. Ultimately, the development of better detection methods may aid in the development of improved predictive models for more targeted therapeutics and in conducting studies to explore the underlying mechanisms of cancer progression.



Dr. Heather Hunt and Ms. Ashley Maker are part of the DNA methylation team.

Leading the Way Toward New Treatments

Richard Gilbertson, M.D., Ph.D. and **Jennifer Atkinson, Ph.D.,** St. Jude Children's Research Hospital, Memphis, Tennessee

Molecular-Targeted Therapies of Childhood Choroid Plexus Carcinoma

Dr. Richard Gilbertson at St. Jude Children's Research Hospital and his colleagues, Drs. David Malkin, R. Kiplin Guy, and David Ellison, have undertaken a herculean effort to improve the treatment of choroid plexus carcinoma (CPC) in pediatric patients. This rare tumor strikes about 50 children a year in the United States, and less than 50% of those children survive. CPC presents a special challenge because of the lack of knowledge, lack of funding, and lack of resources to help these infants and toddlers.

Employing the largest cohort of human CPC tumors from around the world, the multidisciplinary team will generate a catalog of the changes in gene expression and copy number in CPC. This will lead to candidate genes to understand the pathway to carcinogenesis of this tumor type and also provide researchers more targets for lifesaving therapies.

Toward the ultimate goal of clinical development, Dr. Gilbertson and colleagues plan to identify therapeutic lead compounds and to study their antitumor activity in the mouse model for toxicity and long-term effects.

With the FY09 PRCRP Synergistic Idea Award, Dr. Gilbertson's team may discover new treatments, methods, and resources for investigations in CPC.

"My experience in the PRCRP review panel was overall 'excellent.' The dimension added to the discussion by the consumer was helpful as always. The perspective offered by the advocate was from someone who had benefited directly from a therapy similar in nature to what we were discussing, and this made their perspective particularly relevant and welcomed."

R. Jason Stafford, Ph.D.
Peer Review Scientific Reviewer, F09

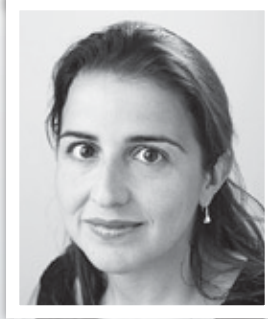
Suzy V. Torti, Ph.D., Wake Forest University Health Sciences, Winston-Salem, North Carolina
Mr. Peter Alexander, predoctoral fellow

Novel Nanoparticle-Based Therapy for Kidney Cancer

Dr. Suzy Torti received a Mentor-Predoctoral Fellow Research Award in FY09, and along with her predoctoral student, Mr. Peter Alexander, is seeking to develop a nanoparticle-based delivery platform for a more robust and superior means of effectively targeting kidney cancer.

The team is proposing to provide a viable new approach to kidney cancer therapy by simultaneously targeting the tumor and its surrounding vasculature with the hope that this "double hit" approach will provide a more effective means of therapy than the conventional anti-cancer therapies. For this "double hit" approach, Dr. Torti plans to combine the tumor-selective peptide D5s and the photothermal ablation properties of nanoparticles and test this combined efficacy *in vitro* in cultured cells and *in vivo* in an orthotopic mouse model of kidney cancer. Dr. Torti hypothesizes that a dual killing effect, initiated by D5s-mediated cytotoxicity and continued by nanoparticle-induced thermal ablation, will result in effective cell death in the tumor and surrounding vasculature. This highly innovative study has the potential, if successful, to have a groundbreaking effect on the therapeutic approach for treatment of kidney cancer and other cancers as well.

Disease Assessment Tools



Iman Osman, M.D., and **Eva Hernando, Ph.D.,** New York University, New York, New York

MicroRNAs Expression Signature Predictive of Melanoma Brain Metastasis

Melanoma preferentially metastasizes to the brain. Patients diagnosed with brain metastasis have a poor prognosis of less than 6 months. An accurate molecular characterization of the mechanisms responsible for brain targeting by melanoma cells is critical for the prevention of brain metastasis.

Recipients of an FY09 Collaborative Translational Science Award, Drs. Eva Hernando and Iman Osman are proposing to identify primary melanoma-specific microRNAs (miRNAs) that are predictive of brain metastasis and to characterize the role of these miRNAs in facilitating B-Met development. Preliminary studies conducted by Drs. Hernando and Osman have identified a set of miRNAs differentially expressed in primary melanoma as well as in melanoma brain metastasis samples. These studies will determine whether a miRNA expression signature is present in melanoma patients who ultimately developed brain metastasis as compared to melanoma patients who developed another type of metastasis. The investigators will also elicit the specific roles of the associated miRNAs in mediating the biological properties that increase brain tropism to melanoma cells. Validation of such biomarkers will aid in pre-metastatic staging of melanoma and identification of those patients who have the highest risk of developing brain metastasis and who may benefit from prophylactic interventions targeting the central nervous system.

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