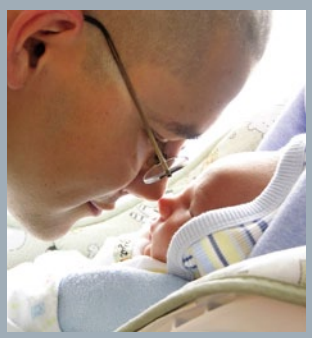
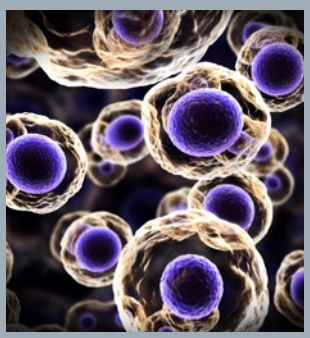
CDMRP

Department of Defense

# Peer Reviewed Cancer Research Program





*U.S. Army Medical Research and Materiel Command*

# Congressionally Directed Medical Research Programs


**Congressional Appropriations for the PRCRP:**

FY09–FY11 – $47 million

FY12 – $12.8 million

## Vision

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

## Mission

Fostering the next generation of cancer research by providing new and early-career investigators opportunities to excel in groundbreaking cutting-edge research for the prevention, detection, and treatment of cancer.

## History

The Office of the Congressionally Directed Medical Research Programs (CDMRP) was established in 1992 from a powerful grassroots effort led by the breast cancer advocacy community that resulted in a congressional appropriation of funds for breast cancer research. This initiated a unique partnership among the public, Congress, and the military that continues today. Since 1992, the CDMRP has grown to encompass multiple research programs and has received nearly $7 billion in appropriations from its inception through fiscal year 2012 (FY12). Funds for the CDMRP are added to the Department of Defense (DOD) budget to support individual programs, such as the Peer Reviewed Cancer Research Program (PRCRP) with specific guidance from Congress.

## Application Review Process

The CDMRP uses a two-tier review process to evaluate applications, with both tiers involving dynamic interaction among scientists, clinicians, and consumer advocates. The first tier of evaluation is a scientific peer review of applications measured against established criteria for determining scientific merit. The second tier is a programmatic review, conducted by the Integration Panel or IP, composed of leading scientists, clinicians, and consumer advocates, which compares applications to each other and makes recommendations for funding based on scientific merit, portfolio balance, and relevance to program goals.

## PRCRP Overview

The Peer Reviewed Cancer Research Program (PRCRP) was established in FY09 to support innovative research in cancers specifically designated by Congress as relevant to military service members and their families. Members of the military are exposed to hazardous environments due to the nature of their service and deployments and, thus, are at risk for the development of different types of cancers. The Veterans Health Administration (VHA) acknowledged the toll of cancer on military service members and their families in its National Cancer Strategy in 2003.[1] In 2007, there were 355,442 military beneficiaries diagnosed with cancer, for a prevalence of 4.1%, composed of over 60 different cancer types.[2] Both a healthy force and family support unit, free of serious illnesses, allows the service member to focus on his or her role as a member of the military and facilitates the overarching mission. Funding studies on the detection, diagnosis, treatment, and prevention of cancer benefits not only the service members and their families, but also the American public. Ultimately, this leads to increased survival rates, improved quality of life, and decreased costs of medical care.

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[1] *VHA-Directive 2003-34.*

[2] *Crawford RS, Wu J, Park D, and Barbour GL. 2007. A study of cancer in the military beneficiary population.* Military Medicine *172:1084-1088.*

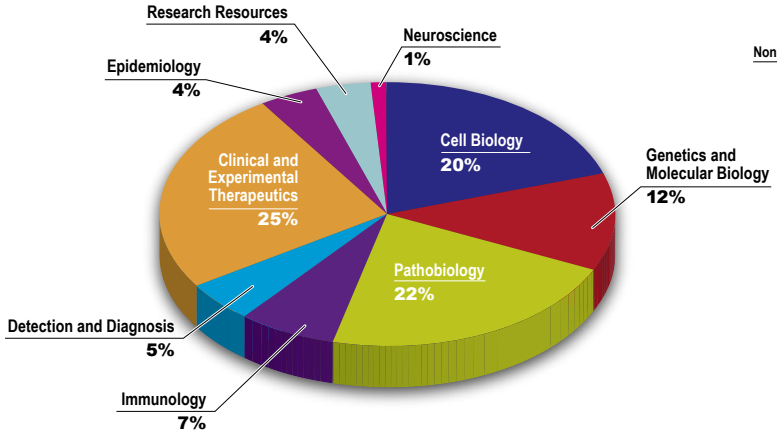
In FY11 and FY12, the PRCRP changed its focus to support exceptionally talented, early-career researchers and clinicians who have the potential to significantly advance the field of cancer research and deliver breakthroughs in the prevention, detection, and treatment of cancer to better the lives of service members, their families, and the American public. By focusing on the next generation of cancer researchers, the PRCRP fosters scientific advancement for military health care and the future of cancer research for the American public.

Specific research topic areas for FY12 are blood cancers, colorectal cancer, genetic cancer research, kidney cancer, Listeria vaccine for cancer, melanoma and other skin cancers, mesothelioma, pancreatic cancer, and pediatric brain tumors.

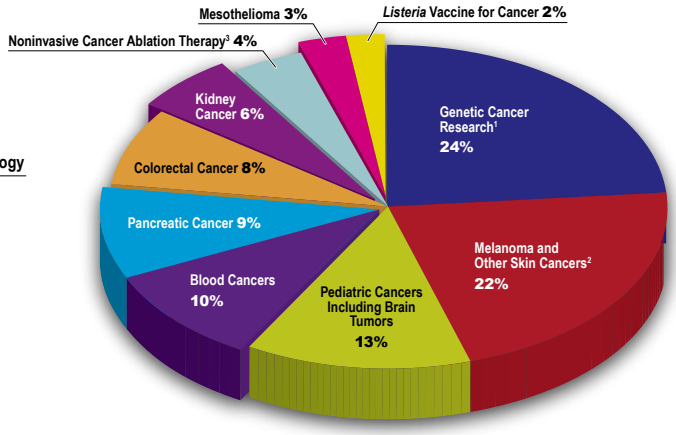
## Portfolio Analysis and Funding History

Through FY09–FY11, PRCRP has offered nine different award mechanisms to support a broad spectrum of research projects in a variety of research disciplines.

**PRCRP FY09–FY11 Portfolio Analysis by Research Area**




**The PRCRP Portfolio Categorized by Percentage of Dollar Amount Invested in Congressionally Directed Topic Areas**
(Updated for FY09–FY11)




"I am so fortunate to have this opportunity to sit on the CDMRP as an active duty Air Force physician. The research that the CDMRP is funding will directly benefit our military members and their families. It has the distinction of being one of the few research programs that focuses on the "underserved" cancer populations, such as children with cancer and adults with less common types of tumors. Since the panel consists of consumer advocates, lab scientists, clinical experts, active duty military providers, and cancer survivors, the discussions regarding the research proposals are excellent, resulting in what we hope will be exciting and innovative treatments for the cancer patient."

**Lt Col Della Howell, M.D.**
Integration Panel Member FY10–FY12

*[1]Topic area includes the FY09 congressional language, genetic cancer and its relation to exposures to the various environments that are unique to the military lifestyle, and the FY10 congressional language, genetic cancer research and genomic medicine.*

*[2]Topic area includes the FY09 congressional language, melanoma and other skin cancers as related to deployments of service members to areas of high exposure, and the FY10 congressional language, melanoma and other skin cancers.*

*[3]Noninvasive cancer ablation treatment including selective targeting with nanoparticles.*

"In today's climate of limited funding prospects for young investigators, it is very important that we put resources into programs that support the future of cancer research. It is a very rewarding experience to be part of a process that puts a major emphasis on supporting early-career cancer researchers."

**Paul Doetsch, Ph.D.**
Integration Panel Member FY10–FY11, and Integration Panel Chair, FY12

"CDMRP offered an opportunity to become more directly involved in colorectal cancer as a consumer reviewer. .....I found that the excellent support provided for consumers and the respectful attitude of the other reviewers helped overcome my initial discomfort. I am happy to be able to represent my fellow colorectal survivors in this very important grant program."

**Michael Katz**
Peer Review Consumer Reviewer, FY10–FY11

# Cancer Incidences in Military Beneficiaries

The 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.

# Malignancies Associated with Military Service

| Exposure or Environmental Toxin | Cancer Type |
|---|---|
| Full-body to nitrogen, sulfur mustard, or nitrogen mustard[1] | Nasopharynx, larynx, lung (except mesothelioma), squamous cell carcinoma of the skin, and acute nonlymphocytic leukemia |
| Ionizing radiation[1,2] | 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 disease), multiple myeloma, primary liver cancer, and bronchioloalveolar carcinoma (a rare lung cancer) |
| Certain herbicide agents[1, 3, 2] | Non-Hodgkin lymphoma, soft-tissue sarcoma (other than osteosarcoma, chondrosarcoma, Kaposi sarcoma, or mesothelioma), Hodgkin 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.)[1, 3, 4, 5] | Melanoma, testicular, thyroid, cervical, vulvar, oral squamous cell, pancreatic, and uterine |


*[1] Crawford RS, Wu J, Park D, and Barbour GL. 2007. A study of cancer in the military beneficiary population. Military Medicine 172:1084-1088.*

*[2] The Selected Cancers Cooperative Study Group. 1990. The association of selected cancers with service in the U.S. military in Vietnam. I. non-hodgkin's lymphoma. Arch Intern Med 150:2473-2483.*

*[3] Department of Defense Automated Central Tumor Registry,http://www.afip.org/consultation/actur/data00.htm.*

*[4] D'Este C, Attia JR, Brown AM, Gibberd R, Tavener M, Guest M, Horsley K, Harrex W, and Ross J. 2008. SHOAMP Study Team. 2008 Cancer incidence and mortality in aircraft maintenance workers. Am J Ind Med 51:16-23.*

*[5] Dalanger NA, Kang HK, and Thomas TL. 1995. Cancer mortality patterns among women who served in the military: The Vietnam Experience. J Occup Environ Med 37:298-305.*

## **Stan Deden,** Peer Review Consumer Reviewer, FY09–FY11

### Learning to Advocate; Advocating to Learn

Even for a medical professional, the disease names were difficult to understand: ideopathic thrombolytic purpura … follicular non-Hodgkin lymphoma. Stan Deden, a nurse anesthetist with 20 years of experience when diagnosed with lymphoma, knew of the disease, but soon realized he had a lot more to learn.

"Prior to my diagnosis, I knew relatively little about lymphoma," Stan said. "I was acquainted with a woman who had been successfully treated for Hodgkin lymphoma in the past and had discussed her treatment and remission with her."

His treatment began 6 months after his diagnosis and involved beam radiation to his chest, abdomen, and pelvis. He remained in remission for 9 years, and following a spontaneous remission in 2005, he continues in remission today.

Stan credits the medical staff at the hospital where he worked and was treated for helping him understand the treatments and making sure it was appropriate. His pathologist and oncologist were attentive and helpful; yet even they could not hide the potential consequences. Stan was told that given his diagnosis and level of care, his immediate future would consist of 3 good years and 2 bad ones.

Advocacy had been on his mind, but any thoughts were put on hold until the treatments were concluded.

"After my initial therapy, my wife and I attended two national-level Patient Education Forums sponsored by the Lymphoma Research Foundation," Stan said. "At the forums, I interacted with other patients with the same diagnosis, and I learned that my diagnosis may not be as grim as I initially had thought."

Stan collected literature about lymphoma and continued to develop knowledge and understanding about the illness. At a second LRF forum, he expressed an interest in a new chapter forming near his home; several months later he was recognized as a founding member of the LRF chapter in Minnesota.

"I realized that my background as a nurse and my disease story would allow me to make a positive connection to newly diagnosed lymphoma patients and make an impact on how they progressed with their disease," Stan said.

In his advocacy work, Stan helps other lymphoma patients find resources that might help alleviate some concerns and fears. Many, like him, have feelings of dread and doom when they are first diagnosed, but learning about treatments and ongoing research helps calm them, and gives them hope for a future. In addition, he works closely with caregivers, making sure they stay engaged and involved with the patient's care.

His ongoing work with the Foundation led to his nomination as a peer reviewer for the Department of Defense Peer Reviewed Cancer Research Program. Stan said he appreciated being able to learn about current and future research and is proud of what he brought to the discussions.

"My background as a nurse, a Vietnam veteran with a military exposure-related cancer, and an advocate for lymphoma has allowed me to represent veterans and lymphoma patients on CDMRP panels in a unique way," Stan said. "My greatest hope as a consumer reviewer is that one day a research proposal that I have reviewed leads to an expanded standard of care procedure or treatment that benefits a wide segment of the community."

And those are words that anyone can understand.

# Developing Diagnostic or Pharmacogenomic Biomarkers

**Deeann Wallis-Schultz, Ph.D.**
Texas A&M University, College Station, Texas

## Identification of Genes Associated with Ionizing Radiation Sensitivity and Resistance

Ionizing radiation is one of the primary treatment modalities for various types of cancer. Ironically, in uncontrolled situations, such as the battlefield or a powerplant leak, it is a carcinogenic hazard for those who are exposed to it. Exposure to radiation causes DNA damage—in clinical settings, radiation is limited to parts of the body that are affected by cancer to reduce unnecessary damage to healthy tissue. Cancer cells, because of their reduced capability for DNA repair, are more sensitive to the effects of ionizing radiation than are normal cells.

Dr. Wallis, recipient of an FY09 PRCRP Concept Award, is working to understand the molecular mechanisms underlying the responses of normal tissues to radiation and to identify critical pathways that are implicated in radiation sensitivity and resistance. Indeed, understanding why genetic variations in individuals may contribute to their sensitivity or resistance to radiation, could allow them to be developed as novel biomarkers to predict radiation response.

With PRCRP support, Dr. Wallis's team developed an entirely novel platform for genomics-based screening utilizing a library of stable mutant murine embryonic stem (ES) cells. These cells come from a library of over 350,000 clones representing nearly 10,000 unique genes. This is a truly unique platform since no one has ever reported a screening of a library of defined mutant ES cells, to find resistance and sensitivity genes. Further, the ES cells offer several advantages over other genomics-based screening technologies. The screen focused on a cancer-relevant subset of the large library and was conducted as a proof-of-concept study to identify genes that play a role in the cells' radiation response. Although the study is ongoing, Dr. Wallis' team has already identified 7 genes that are involved in radiation resistance and of these, 4 have never been implicated in radiation response before. Specific clones can be utilized immediately and evaluated in multiple tissue types in vitro or in vivo by generating a mutant (knock out) mouse. These mice would serve as new models to further radiation research. The results of this study will be used to develop novel strategies for increasing radiation therapy efficacy in cancer patients as well as strategies for enhancing radiation resistance for military personnel who are at risk for radiation exposure in the battlefield. Utilization of this platform has also been expanded to studies involving select agent screenings in a Defense Threat Reduction Agency-funded project.

Steven Silverstein and family

"The management of the PRCRP is conducted by a highly motivated, dedicated, and thoughtful staff of professionals pursuing their work with greatest spirit of integrity.

The panel members approach their work reviewing and ranking the proposals with a tremendous sense of responsibility, sincerity, and a genuine collaborative spirit to select the most appropriate and exciting proposals.

What results is a highly effective process, which allocates these precious resources in alignment with the congressional mandates."

**Steven Silverstein, M.B.A.**
Integration Panel Consumer Member, FY10–FY12

## UV Light May Induce Prolonged DNA Damage in Melanocytes Days After Exposure

Exposure to sunlight is the major cause of melanoma, particularly in fair-skinned individuals. Ultraviolet light (UVL) within sunlight can directly damage the DNA of melanocytes (pigment cells responsible for producing melanin). Moreover, reactive oxidative species (ROS) can form as a byproduct of melanin, causing further damage to the DNA.

Drs. Halaban, Brash, and Bosenberg of Yale University, recipients of an FY09 PRCRP Collaborative Translational Science Award, hypothesize that individuals at high risk for developing melanoma have melanocytes that are particularly susceptible to UVL-mediated DNA damage because of a reduced ability to sequester ROS, which leads to harmful DNA mutations and epigenetic modifications. Since epigenetic modifications are passed from parental cells to daughter cells, the melanocytes progressively accumulate these altered DNA control settings over multiple cycles of cell division, leading to an increased risk for melanoma.

With PRCRP support, the investigators are currently identifying ROS- and UVL-dependent epigenetic changes in melanocytes. Results thus far have demonstrated that, in mice, exposure to UVL leads to an altered epigenetic profile. In addition, melanin alters the kinds of DNA damage found in melanocytes. The long-term effects of sun damage may be related to these processes of DNA control and DNA damage.

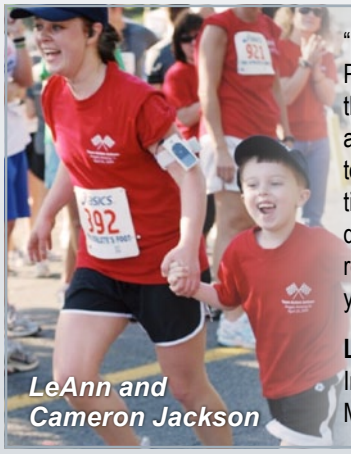
This study may lead to the development of genetic markers that can identify individuals at high risk of sunlight-induced melanoma, as well as strategies for preventing DNA alterations after sun exposure. These genetic markers and preventive strategies may be especially impactful for soldiers on the battlefield, who are often exposed to long hours in the sun and may not have access to adequate sun protection.

**Ruth Halaban, Ph.D.,**
Department of Dermatology;

**Douglas Brash, Ph.D.,**
Departments of Dermatology, Genetics and Therapeutic Radiology;

**Marcus Bosenberg, M.D., Ph.D.,**
Department of Dermatology;

Yale University School of Medicine, New Haven, Connecticut



*LeAnn and Cameron Jackson*

"Serving as a consumer advocate on the Integration Panel for PRCRP has enabled me to be a voice from the cancer community, representing pediatric patients and their families. It has been an incredible experience to partner with both clinicians and scientists in an attempt to make a difference in the field of cancer research both now and for years to come."

**LeAnn Jackson, B.A.**
Integration Panel Consumer Member, FY10–FY12

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