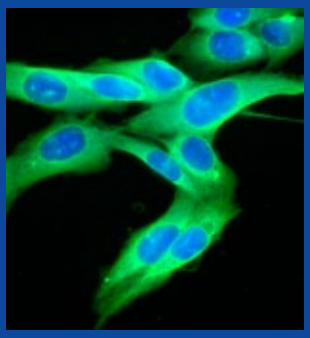
CDMRP

Department of Defense

Peer Reviewed Cancer Research Program



U.S. Army Medical Research and Materiel Command

PROTECT · PROJECT · SUSTAIN

Congressionally Directed Medical Research Programs

Background

The Office of the Congressionally Directed Medical Research Programs (CDMRP) was established in 1992 due to 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. Funds for the CDMRP are added to the Department of Defense budget to support individual programs, such as the Peer Reviewed Cancer Research Program (PRCRP), with specific guidance from Congress. The PRCRP was established in fiscal year 2009 (FY09) to support innovative and impactful research in cancers specifically designated by Congress as relevant to military service members, their families, and other military beneficiaries. Appropriations for the PRCRP from FY09 through FY13 totaled $74.8 million (M). The FY14 appropriation is $25M.

The Program Cycle

The PRCRP holds an annual vision setting meeting to identify research gaps and define an investment strategy for the program year. Vision setting is conducted by the Integration Panel (IP), comprised of experts including scientists, clinicians, and consumers (patients, advocates, and caregivers affected by cancer). The IP recommends an investment strategy that encourages research in underfunded and unrepresented areas that are considered most critical to the program and advance cancer research, and that answer the needs of the military and the American public.

The PRCRP utilizes the CDMRP's two-tier review of applications that is based on the recommendations set forth by the Institute of Medicine committee in 1993. The two tiers of review are peer review and programmatic review. Although the two tiers have different goals, they are complementary. Peer review, the first tier of application evaluation, is a scientific peer review of applications measured against established criteria for determining scientific merit. Programmatic review, the second tier of application evaluation, is conducted by the IP, which compares applications to each other and makes recommendations for funding based on scientific merit, portfolio balance, and relevance to program goals.

The Peer Reviewed Cancer Research Program Mission

The Veterans Health Administration (VHA) identified malignancies that may be associated with military service (VHA-Directive 2003-34). Exposure to chemical weapons, or storage, ionizing radiation, herbicides, electromagnetic fields, jet fuel, organic materials, etc. have been linked to different malignancies (see table on following page). A serious illness in a family member, such as cancer, may significantly impact the warfighter's ability to complete the mission. A healthy family unit, free of serious illnesses, allows the service member to focus on his or her role as a warfighter and facilitates the overarching military mission. There are over 355,000 military beneficiaries with a cancer diagnosis, for a prevalence of 4.1%, comprised of over 60 different cancer types. The cost of cancer care within the military health system is in the billions[1].

Throughout the years, Congress has charged the PRCRP to study various cancers and topic areas in cancer research. Investment in these different areas of research focuses on basic, applied, and translational studies. Funding studies on the prevention, early detection, diagnosis, and treatment of these diseases benefits the warfighter and the American public, ultimately leading to increased survival rates and decreased costs of medical care.

Military Relevance and Cancer Research

In FY13 and FY14, the PRCRP offered the Idea Award with Special Focus award mechanism, intended to support innovative research relevant to active duty service members, their families, and other military beneficiaries. The "special focus" of this award mechanism is on the cancers associated with exposures, conditions, or circumstances that are unique to the military or disproportionately represented within the military beneficiary population. Applications for the FY14 Idea Award with Special Focus were required to address at least one of the following Military Relevant Focus Areas listed below:

- Assessment of militarily relevant risk factors (e.g., ionizing radiation, chemical, and environmental carcinogens) associated with the susceptibility, early detection, progression, and treatment of cancer.
- Examination of cancer diagnosis and prognosis effects on the psychosocial well-being of military members and their beneficiaries.
- Gaps in cancer prevention, diagnosis, early detection, or treatment that may affect the general population but have a particularly profound impact on military health.

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

Vision

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

Mission

To foster the next generation of cancer research by providing new opportunities to successfully pursue high-impact research for the prevention, detection, and treatment of cancer.

Congressional appropriations for the PRCRP:
FY14 – $25M

Malignancies Associated with Military Service[2]

Members of the military are exposed to hazardous environments and dangerous deployments due to the nature of their service[3]. Hazardous exposures can lead to the development of various cancers, many of which present a potential risk for service members and their families. The table below outlines many potential hazards identified in the environment that service members may be at higher risk of encountering.

Exposure Type	Cancer Type
Full body to Nitrogen, Sulfur Mustard, or Nitrogen Mustard[4]	Nasopharynx, larynx, lung (except mesothelioma), squamous cell carcinoma of the skin, and acute nonlymphocytic leukemia
Ionizing Radiation[4,5]	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[4-6]	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.)[4-8]	Melanoma, testicular, thyroid, cervical, vulvar, oral squamous cell, pancreatic, and uterine
Infectious agents[9]	Gastric adenocarcinoma, cervical cancer, vaginal and vulva cancer, hepatocarcinoma, head and neck cancers, penile cancer, and anal cancer

[2] VHA-Directive 2003-34.

[3] Bullman TA and Kang HK. 1994. The effects of mustard gas, ionizing radiation, herbicides, trauma, oil smoke on US military personnel: The results of veteran studies. *1994 Ann Rev Pub Health* 15:69-90.

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

[5] 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.

[6] Department of Defense Automated Central Tumor Registry.

[7] 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.

[8] 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.

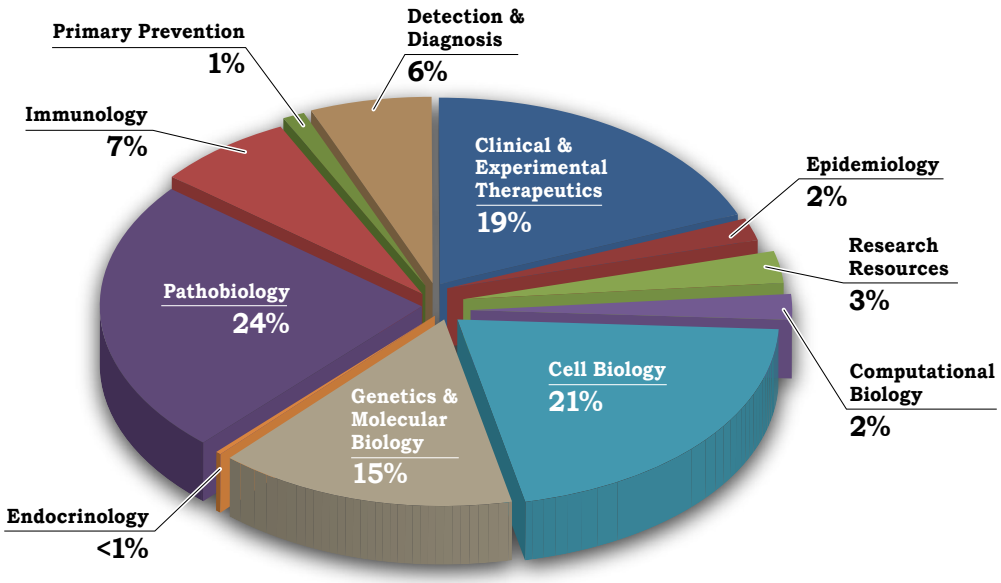
[9] Piazuelo MB, Epplein M, and Correa P. 2010. Gastric cancer: An infectious disease. *Infect Dis. Clin North Am* 24:853-869.

http://www.cdc.gov/hpv/cancer.html.

PRCRP Invests in Different Types of Cancer

Since its inception, the PRCRP has solicited research projects in 15 congressionally directed topic areas spanning a wide range of cancer types, but excluding breast, lung, ovarian, and prostate cancers, which have individual programs with missions dedicated to their eradication. In each fiscal year, the PRCRP receives its funds and topic areas through the annual congressional legislation known as the Defense Appropriations Act. The dollars to fund PRCRP are added every year during the budget approval cycle by the members of the House or Senate in response to requests by the American public (consumer advocates, disease survivors, caregivers); therefore, topic areas can vary from year to year. A complete listing of topic areas may be found at http://cdmrp.army.mil/prcrp/topicareas/topicareas.shtml.

The areas of research for the PRCRP vary but include basic, applied, and translation studies.



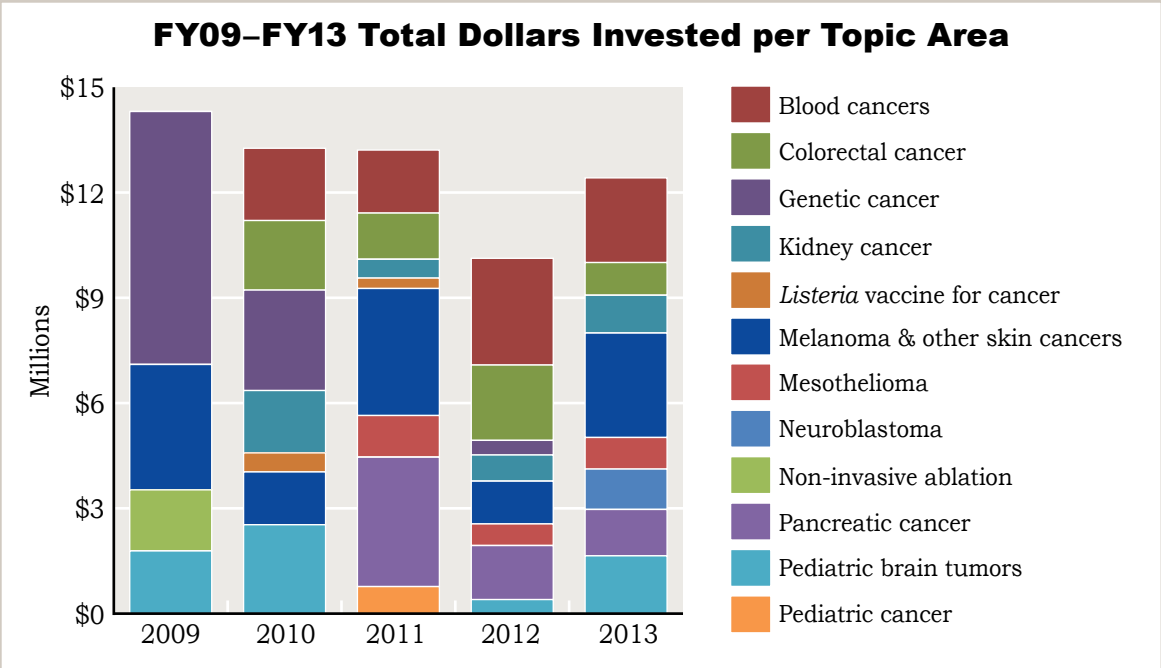
"As an active duty physician and cancer researcher, I am honored to participate in the CDMRP Peer Reviewed Cancer Research Program. The diverse members of the Integration Panel bring a dedication and passion to the process that ensures its integrity. I have no doubts that this program is fulfilling its charge of supporting the most promising investigators and research. In the long term, I absolutely believe that those we support today will positively impact cancer care and truly make a difference for my fellow service members and their families."

Lt. Col. Chad A. Hamilton, M.D.
Walter Reed National Military Medical Center
FY13–FY14 IP Member

FY09–FY13 PRCRP Research Portfolio Investments per Topic Area

Congressional language directs the research topic areas to be included in the PRCRP. Each fiscal year, the topic areas change according to the current needs of the military, or in answer to an identified research gap. The table below illustrates the investment per dollars in each topic area per fiscal year.

Topic Area[a, b]	FY09[h]	FY10	FY11	FY12	FY13
Blood cancers	$0	$2,059,253	$1,795,508	$3,041,168	$2,412,520
Colorectal cancer	$0	$1,982,333	$1,316,840	$2,146,329	$932,615
Genetic cancer[c]	$7,209,151	$2,862,226	$0	$417,501	$0
Kidney cancer	$0	$1,776,990	$536,000	$746,160	$1,077,558
Listeria vaccine for cancer	$0	$543,200	$296,000	$0	$0
Melanoma and other skin cancers[d]	$3,572,366	$1,504,374	$3,619,650	$1,218,000	$2,974,619
Mesothelioma	$0	$0	$1,188,720	$616,613	$900,468
Neuroblastoma[e]	$0	$0	$0	$0	$1,151,460
Non-invasive ablation[f]	$1,741,070	$0	$0	$0	$0
Pancreatic cancer	$0	$0	$3,686,682	$1,539,122	$1,320,878
Pediatric brain tumors	$1,786,229	$2,532,910	$0	$400,425	$1,647,150
Pediatric cancer	$0	$0	$770,586	$0	$0
Radiation protection utilizing nanotechnology	$0	$0	$0	$0	$0
Totals[g]	**$14,308,816**	**$13,261,286**	**$13,209,986**	**$10,125,318**	**$12,417,268**



[a] No full applications were submitted for radiation protection utilizing nanotechnology (offered in FY10–FY11).

[b] Cancers related to radiation exposure and myeloproliferative disorders were introduced in FY14 (FY14 negotiations are not yet finalized).

[c] Topic area includes 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.

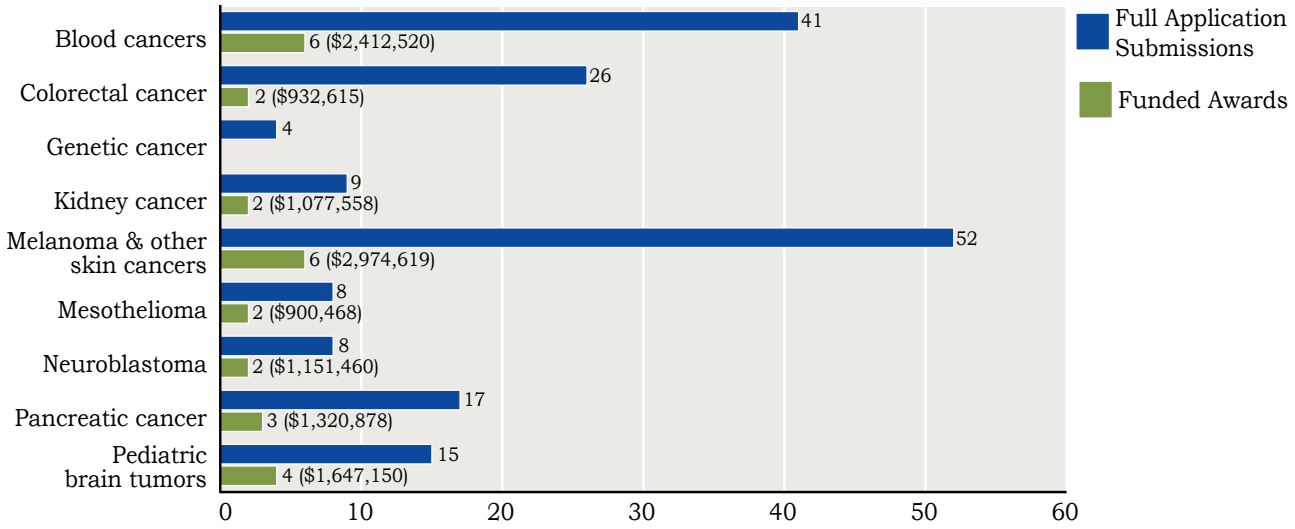
[d] Topic area includes FY09 congressional language: melanoma and other skin cancers as related to deployments of service members to areas of high exposure; and the FY10 congressional language: melanoma and other skin cancers.

FY13 PRCRP Research Portfolio Funding Investments

FY13 PRCRP Receipt and Funding Summary

Topic Area	Dollars Invested	Compliant Submissions	Fund	Not Fund	Withdrawn
Blood cancers	$2,412,520	41	6	34	1
Colorectal cancer	$932,615	26	2	23	1
Genetic cancer	$0	4	0	4	0
Kidney cancer	$1,077,558	9	2	6	1
Listeria vaccine for cancer	$0	0	0	0	0
Melanoma & other skin cancers	$2,974,619	52	6	45	1
Mesothelioma	$900,468	8	2	6	0
Neuroblastoma	$1,151,460	8	2	6	0
Pancreatic cancer	$1,320,878	17	3	14	0
Pediatric brain tumors	$1,647,150	15	4	11	0
Totals	**$12,417,268**	**180**	**27**	**149**	**4**

FY13 PRCRP Number of Awards and Investments per Topic Area



Genetic cancer: None of the 4 compliant submissions in this topic area were recommended for funding.
Listeria vaccine for cancer: No compliant submissions for this topic area were received in FY13.

[e] Topic area was introduced in FY13.

[f] Non-invasive cancer ablation treatment including selective targeting with nanoparticles.

[g] Total appropriations for FY09–FY12 were $59.8M; total investment in research dollars is less U.S. Army Medical Research and Materiel Command (USAMRMC) and CDMRP management costs (12.1%) and FY12 sequestration costs ($938,860). Total appropriation for FY13 was $15.0M; total investment in research dollars is less USAMRMC and CDMRP management costs (8.9%) and FY13 sequestration costs ($1.211M).

[h] In FY09, Congress directed PRCRP to offer four topic areas with specific budgets: (1) Genetic cancer research and its relation to exposure to the various environments that are unique to a military lifestyle ($8M); (2) Melanoma and other skin cancers as related to deployments of service members to areas of high exposure ($4M); (3) Non-invasive cancer ablation treatment research including selective targeting with nanoparticles ($2M); and (4) Pediatric brain tumors within the field of childhood cancer ($2M).

Peer Reviewed Cancer

BLOOD CANCER

Drs. Gregory Lanza (left) and **Michael Tomasson** (right) developed a nanoparticle-delivered prodrug to inhibit Myc and treat multiple myeloma. The prodrug has shown improved bioactivity when compared to the free drug and has extended survival by 50% in a murine model of the metastatic disease.

Dr. Aaron Newman developed a novel method to determine response to treatment in patients with follicular lymphoma. By using this new computational methodology, he found that the frequency of a distinct immune cell type and sequence features of patient immunoglobulins are potential predictive biomarkers.

http://cdmrp.army.mil/prcrp/research_highlights/13newman_alizadeh_highlight.shtml

Dr. Yue Wei demonstrated that abnormal activation of innate immunity signaling is involved in the pathogenesis of Myelodysplastic syndrome (MDS). Toll-like receptor and inflammation associated with histone demethylase JMJD3 has been shown to be deregulated in hematopoietic stem cells in MDS. Inhibition of Toll-like receptor 2, JMJD3, and inflammatory cytokines improved hematopoietic differentiation.

Wei Y, Chen R, et al. 2013. *Global H3K4me3 genome mapping reveals alterations of innate immunity signaling and overexpression of JMJD3 in human myelodysplastic syndrome CD34+ cells.* Leukemia 27(11):2177-86.

Wei Y, Dimicoli S, Bueso-Ramos C, et al. 2013. *Toll-like receptor alterations in myelodysplastic syndrome.* Leukemia 27(9):1832-1840.

COLORECTAL CANCER

Dr. Lee Ellis demonstrated the endothelial cells secrete factors (specifically soluble Jagged-1) to promote the cancer stem cell phenotype of colorectal cancer cells without cell-to-cell contact via Notch activation. This is in contrast to the classic model of Notch signaling requiring cell-to-cell contact. With this finding, it may be possible to develop therapeutics based on targeting soluble Jagged-1 that may be less toxic than current Notch inhibitors.

Lu J, Ye X, et al. 2013. *Endothelial cells promote the colorectal cancer stem cell phenotype through a soluble form of Jagged-1.* Cancer Cell 23(2):171-85.

Dr. Mansour Mohamadzadeh found that a LTA-deficient *L.acidophilus* regulates inflammation and protects against colonic polyposis in a murine model. This discovery may lead to an oral therapeutic to prevent the initiation of colorectal cancer.

Khazaie K, Zadeh M, Khan MW, et al. 2012. *Abating colon cancer polyposis by Lactobacillus acidophilus deficient in lipoteichoic acid.* Proc Natl Acad Sci U S A 109(26):10462-10467.

Research Achievements

GENETIC CANCER

Dr. Ann-Marie Broome identified CD15 as a biomarker for cancer stem cells in specific medulloblastoma animal models and discovered that only cancer stem cells with activated EMT pathways can initiate metastatic disease.

Anges RS, Broome AM, et al. 2012. *An optical probe for noninvasive molecular imaging of orthotopic brain tumors overexpressing epidermal growth factor receptor.* Mol Cancer Ther 11(10):2202-11.

KIDNEY CANCER

Dr. Srikanth Singamaneni introduced a paper-based localized surface plasmon resonance substrate that enabled the detection of aquaporin-1, urinary biomarker for kidney cancer down to 10ng/ml.

Gandra N and Singamaneni S. 2013. *Surface enhanced Raman scattering for in vivo imaging: The future looks BRIGHT?* Nanomedicine 8:317.

MELANOMA and OTHER SKIN CANCERS

Drs. Eva Hernando (left) and **Iman Osman** (right) performed microRNA analysis of human melanoma and found high expression of miR-30b/30d correlated with metastatic potential and shorter time to recurrence as well as a reduced overall survival. Moreover, they proved that this miRNA promotes cell invasion *in vitro* and metastasis *in vivo* using animal models, therefore showing that miR-30b/30d may have a key role in metastasis.

Gaziel-Sorvan A, Segura MF, et al. 2011. *miRNA-30b/30d regulation of GAlNAc transferase enhances invasion and immunosuppression during metastasis.* Cancer Cell 20(1):104-18.

Dr. Andrew Aplin established an *in vivo* extracellular signal-regulated kinases (ERK)1/2 reporter system to provide temporal and quantitative analysis of ERK activity during response and resistance to RAF inhibitors in the treatment of melanoma. The studies showed that RAS mutations and BRAF splice variants reactivate the ERK1/2 pathway that leads to RAF inhibitor resistance in mutant BRAF cells.

Kaplan FM, Kugel CH, Dadpey N, et al. 2012. *SHOC2 and CRAF mediate ERK1/2 reactivation in mutant NRAS-mediated resistance to RAF inhibitor.* J Biol Chem 287:41797-41807.

Research Achievements (cont.)

MESOTHELIOMA

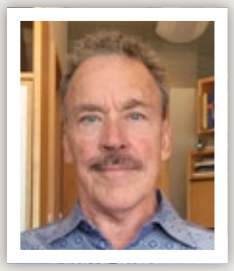
Dr. Bruce Robinson showed that targeted removal of Treg, particularly during early tumor development, can significantly enhance anti-tumor immunity, thus delaying tumor development in a mesothelioma mouse model.

NON-INVASIVE CANCER ABLATION

Dr. Michael Gach demonstrated RF heating of single-wall carbon nanotubes using magnetic resonance imaging and the potential to generate targeted hyperthermia.

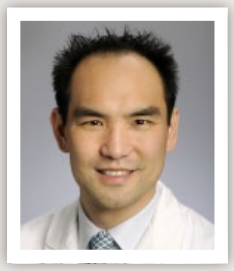
Nair T, Symanowski JT, and Gach HM. 2011. *Comparison of complex permittivities of isotonic colloids containing single-wall carbon nanotubes of varying chirality.* Bioelectromagnetics 10.1002/bem 20689.

PANCREATIC CANCER



Dr. Robert Fletterick screened over 5 million compounds to find the first antagonists of liver receptor homolog 1 (LRH1), that regulates functions of the liver, intestines, and pancreas, and can be associated with tumorigenesis. The candidates identified inhibit LRH1 transcriptional activity and decrease the receptor's target gene expression. These could be novel agents for pancreatic cancer therapeutics.

Benod C, Carlsson J, et al. 2013. *Structure-based discovery of antagonists of nuclear receptor LRH1.* J Biol Chem 288(27):19830-44.

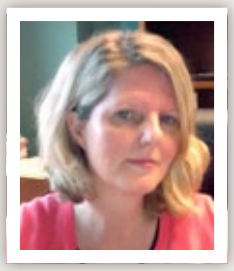


Dr. David Yu identified CHD7 as a novel biomarker candidate for predicting gemcitabine response for early-stage resected pancreatic ductal adenocarcinoma patients and discovered low CHD5 expression predicts poor outcomes in resected pancreatic cancer patients.

Colbert LE, Petrova AV, et al. 2014. *CHD7 expression predicts survival outcomes in patients with resected pancreatic cancer.* Cancer Res 74(10):2677-87.

Hall WA, Petrova AV, et al. 2013. *Low CHD5 expression activates the DNA damage response and predicts poor outcome in patients undergoing adjuvant therapy for resected pancreatic cancer.* Oncogene 10.1038.

PEDIATRIC BRAIN TUMOR/ PEDIATRIC CANCERS



Dr. Tracy-Ann Read identified CD15 as a potential biomarker for cancer stem cells in a specific medulloblastoma animal model, and she discovered that only smo/smo mice that expressed Math1, Nestin, and CD15 in medulloblastoma progressed to metastatic disease.

Consumer Perspectives

Elizabeth Naylor

Elizabeth Naylor was diagnosed with primary mediastinal diffuse large B-cell lymphoma in October 2009. She endured three different types of chemotherapy, and when each failed, she went through an experimental allogenic stem cell transplant before reaching partial remission with no sign of cancer activity. “Cancer diagnosis,” Elizabeth states, “has caused me to live my life more deliberately and with more awareness of little things. Cancer scared me like nothing else and every day I work to remember that I am in control and I can make choices about my life.”

Elizabeth has become active in the advocacy community hoping to ease others’ journeys through cancer diagnosis and treatment. As an Ambassador for the Lymphoma Research Foundation, she spends her free time connecting with other patients and survivors, as well as caregivers and healthcare providers. She also served as a consumer peer reviewer for the PRCRP, which has been an empowering experience. “It means so much to have been given a voice in something that is a part of my life. I truly appreciate that the scientific community has been receptive to hearing the stories of myself and other consumer reviewers.”

Jose Silveiras

Jose Mendoza Silveiras was diagnosed with stage 2 colorectal cancer in 2008 at age 32. Although he had a family history of colorectal cancer, he did not think he needed to worry about it until he was older – something he now wants others to avoid.

Since his diagnosis, Jose has devoted his free time to community volunteering for minorities for prevention of diseases. He serves as a Scientific Advisory Member for the Colon Cancer Alliance, and is a Patient Representative Advocacy Consultant for the FDA. He describes his experience as a PRCRP consumer peer reviewer as “incredible,” and feels that the scientist/clinician reviewers are committed to understanding cancer and how it is to live with a cancer diagnosis. Jose states: “This mission is a work in progress; we need more people willing to share their experiences and be able to help in the advancement of cancer research for the generations to come.”

For more information, visit
http://cdmrp.army.mil
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