DoD Peer Reviewed Cancer Research Program (PRCRP)

Each year, the Department of Defense's office of the Congressionally Directed Medical Research Programs (CDMRP) assesses scientific opportunities to advance research in specific areas. The investigators supported by individual programs are making significant progress against targeted diseases, conditions, and injuries. This list is not intended to be a full representation of accomplishments, but rather a sampling of the broad portfolio of research and advances resulting from congressional appropriations.

Year	Cancer Type	PRCRP Research Contributions	Additional Information and Hyperlinks
2009	Genetic Cancer	Dr. Ying-Hsui Su developed a probe-mediated PCR assay specific for a DNA marker, hypermethylated vimentin gene, to detect colorectal cancer in urine samples.	• Song BP, Jain S, et al. 2012. Detection of hypermethylated vimentin in urine of patients with colorectal cancer. J Mol Diagn 14(2):112-19.
2009	Genetic Cancer	Dr. Joanna Kitlinska demonstrated that neuropeptide Y (NPY) and other stress mediators have potent effects on tumor development and progression. Animal model studies have shown the role of NPY in the initiation and/or development of leukemia/lymphoma, angiosarcoma, folliculoma, and the stimulatory effect on already established tumors.	• Tilan J and Kitlinska J. 2010. Sympathetic neurotransmitters and tumor angiogenesis-link between stress and cancer progression. J Oncol 539706. • Tilan J and Kitlinska J. 2016. Neuropeptide Y (NPY) in tumor growth and progression: Lessons learned from pediatric oncology. Neuropeptides 55:55-66. • Paiva SP, Veloso CA, et al. 2016. Elevated levels of neuropeptide Y in preeclampsia: A pilot study implicating a role for stress in pathogenesis of the disease. Neuropeptides 55:127-35. • Hong SH, Tilan JU, et al. 2015. High neuropeptide Y release associates with Ewing sarcoma bone dissemination - in vivo model of site-specific metastases. Oncotarget 6(9):7151-65. • Tilan JU, Krailo M, et al. 2015. Systemic levels of neuropeptide Y and dipeptidyl peptidase activity in patients with Ewing sarcoma--associations with tumor phenotype and survival. Cancer 121(5):697-707.
2009	Genetic Cancer	Dr. Wenwei Hu studied the link between chronic stress, radiation exposure, and cancer development, showing that chronic stress elevated glucocorticoid levels that induce SGK1 to negatively inhibit p53 and in turn promote tumorigenesis.	• Feng Z, Liu L, et al. 2012. Chronic restraint stress attenuates p53 function and promotes tumorigenesis. Proc Natl Acad Sci USA 109(18):7013-18. • Yue X, Zhao Y, et al. 2015. BAG2 promotes tumorigenesis through enhancing mutant p53 protein levels and function. Elife 4. • Zhang C, Liu J, et al. 2016. microRNA-1827 represses MDM2 to positively regulate tumor suppressor p53 and suppress tumorigenesis. Oncotarget 7(8):8783-96. • Zheng T, Wang J, et al. 2013. Spliced MDM2 isoforms promote mutant p53 accumulation and gain-of-function in tumorigenesis. Nat Commun 4:2996.

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2009	Melanoma and Other Skin Cancers	Drs. Eva Hernando and Iman Osman 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 play 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. • Fleming NH, Zhong J, et al. 2015. Serum-based miRNAs in the prediction and detection of recurrence in melanoma patients. Cancer 121(1):51-9.
2009	Melanoma and Other Skin Cancers	Melanin polymers are effective absorbers of UV light, letting them protect the skin against sunlight. However, Dr. Douglas Brash and his team found that melanin contributes to DNA damage in the absence of direct UV exposure. The properties of melanin which make it a good UV absorber also make it susceptible to chemical reactions that, in the end, have potentially harmful results similar to overexposure to UV radiation. Using biochemistry, photochemistry, and excited-state chemistry, Dr. Brash's group was able to determine the chemical pathway and find potential avenues for treatment of UV damage after sun exposure.	• Premi S, Wallisch S, et al. 2015. Photochemistry. Chemiexcitation of melanin derivatives induces DNA photoproducts long after UV exposure. Science 347(6224):842-7. • PRCRP Research Highlight • Williams SCP. 2015. You can still get skin cancer in the shade. Science DOI: 10.1126/science.aaa7881
2009	Non-Invasive Cancer Ablation	Dr. Michael Gach demonstrated RF heating of single-wall carbon nanotubes using an MRI 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.
2009	Non-Invasive Cancer Ablation	Over the course of this award, Dr. Anthony Berdis from Case Western Reserve University synthesized several novel gold-containing anti-cancer agents and demonstrated that these compounds could reduce cancer growth, with minimal signs of toxicity, when combined with clinically relevant doses of ionizing radiation. This combination could provide a new strategy to noninvasively ablate tumors.	• Craig S, Gao L, et al. 2012. Gold-containing indoles as anticancer agents that potentiate the cytotoxic effects of ionizing radiation. J Med Chem 55(5):2437-51.
2009	Pediatric Brain Cancer	Drs. Richard Gilbertson, David Malkin, Rodney Guy, and David Ellison defined the molecular landscape for choroid plexus carcinoma, a rare type of pediatric brain tumor with no treatment advances in the last 25 years and a high mortality rate. Identification of gene alterations assisted in the search for different drugs and led to a screen of over 1.2 million compounds identifying gemicitabine as a candidate treatment that is progressing toward clinical trials.	• PRCRP Research Highlight • Tong Y, Merino D, et al. 2015. Cross-species genomics identifies TAF12, NFYC, and RAD54L as choroid plexus carcinoma oncogenes. Cancer Cell 27(5):712-27. • Merino DM, Shlien A, et al. 2015. Molecular characterization of choroid plexus tumors reveals novel clinically relevant subgroups. Clin Cancer Res 21(1):184-92.
2010	Blood Cancer	Drs. Gregory Lanza and Michael Tomasson 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 it extended survival by 50% in a murine model of the metastatic disease.	• Soodgupta D, Pan D, et al. 2015. Small molecule MYC inhibitor conjugated to integrin-targeted nanoparticles extends survival in a mouse model of disseminated multiple myeloma. Mol Cancer Ther 14(6):1286-94.

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2010	Colorectal Cancer	Dr. Lee Ellis demonstrated that 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. • Wang R, Ye X, et al. 2016. A disintegrin and metalloproteinase domain 17 regulates colorectal cancer stem cells and chemosensitivity via Notch1 signaling. Stem Cells Transl Med 5(3):331-8.
2010	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, 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.
2010	Genetic Cancer	Drs. Robert Moritz, Leroy Hood, Gregory Foltz, and Charles Cobbs from the Institute for Systems Biology and the Swedish Neuroscience Institute developed techniques in proteogenomic analysis for whole-genome sequencing of cancer patients' tumors, individual quantized tumor cells, non-cancerous cells, and non-cancerous cells from the patients' family members to perform inheritance analysis and identify candidate genes involved in neoplastic glioblastoma formation. These techniques, combined with proteomic analysis tools, have led to the identification of perturbed networks of genes, providing promising insights for the discovery of novel targeted therapeutics for glioblastoma and identification of novel blood biomarkers for early detection.	• Roach JC, Glusman G, et al. 2010. Analysis of genetic inheritance in a family quartet by whole-genome sequencing. Science 328(5978):636-9. • Li XJ, Hayward C, et al. 2013. A blood-based proteomic classifier for the molecular characterization of pulmonary nodules. Sci Transl Med 5(207):207ra142.
2010	Kidney Cancer	Dr. Srikanth Singamaneni introduced a paper-based localized surface plasmon resonance (LSPR) substrate that enabled the detection of aquaporin-1 (AQP1), a 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(3):317-20.
2010	Kidney Cancer	Drs. Muneesh Tewari and Allan Pantuck demonstrated that miRNA-210 was elevated in serum of kidney cancer patients, and they identified seven additional miRNAs as potential serum biomarkers. They also optimized a method of digital PCR for highly precise serum microRNA measurement.	• Hindson CM, Chevillet JR, et al. 2013. Absolute quantification of low abundance targets by droplet digital PCR versus analog real-time PCR. Nat Methods 10(10):1003-05. • Chevillet JR, Kang Q, et al. 2014. Quantitative and stoichiometric analysis of the microRNA content of exosomes. Proc Natl Acad Sci U S A 111(41):14888-93.
2010	Listeria Vaccine for Cancer	A promising approach to cancer treatment is to make vaccines using specialized cells of the immune system called dendritic cells. Dr. David Chung from Memorial Sloan-Kettering Cancer Center found that a noninfectious strain of Listeria monocytogenes bacteria could activate dendritic cells while avoiding excessive activation of immune-dampening factors that could impede vaccine responses. These results support the use of Listeria to boost dendritic cell vaccine efficacy.	• Chung DJ, Romano E, et al. 2013. Langerhans-type and monocyte-derived human dendritic cells have different susceptibilities to mRNA electroporation with distinct effects on maturation and activation: implications for immunogenicity in dendritic cell-based immunotherapy. J Transl Med 11:166.

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2010	Melanoma and Other Skin Cancers	Dr. Andrew Aplin established an in vivo ERK1/2 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, et al. 2012. SHOC2 and CRAF mediate ERK1/2 reactivation in mutant NRAS-mediated resistance to RAF inhibitor. J Biol Chem 287:41797-807.
2010	Pediatric Brain Cancer	Dr. Amy Keating published studies detailing the development of a xenograft model of human glioma, and how a commercially available small molecule inhibitor of Mer and Axl (two receptor tyrosine kinases overexpressed in glioma) leads to enhanced tumor cell death.	• Knubel KH, Pernu BM, et al. 2014. MerTK inhibition is a novel therapeutic approach for glioblastoma multiforme. Oncotarget 5(5):1338-51. • Pierce AM and Keating AK. 2014. TAM receptor tyrosine kinases: Expression, disease and oncogenesis in the central nervous system. Brain Res 13(1542):206-20.
2011	Blood Cancer	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.	• PRCRP Research Highlight • Newman AM, Liu CL, et al. 2015 Robust enumeration of cell subsets from tissue expression profiles. Nat Methods 12(5): 453-7.
2011	Blood Cancer	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, et al. 2013. Toll-like receptor alterations in myelodysplastic syndrome. Leukemia 27(9):1832-40.
2011	Colorectal Cancer	Dr. Mansour Mohamadzadeh found that an 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, et al. 2012. Abating colon cancer polyposis by Lactobacillus acidophilus deficient in lipoteichoic acid. Proc Natl Acad Sci USA 109(26):10462-67. • Lightfoot YL, Selle K, et al. 2015. SIGNR3-dependent immune regulation by Lactobacillus acidophilus surface layer protein A in colitis. EMBO J 34(7):881-95. • Sahay B, Ge Y, et al. 2015. Advancing the use of Lactobacillus acidophilus surface layer protein A for the treatment of intestinal disorders in humans. Gut Microbes 6(6):392-7. • Lightfoot YL, Yang T, et al. 2014. Colonic immune suppression, barrier dysfunction, and dysbiosis by gastrointestinal bacillus anthracis Infection. PLoS One 9(6):e100532.
2011	Melanoma and Other Skin Cancers	Dr. Margaret Callahan has investigated the immunologic effects of BRAF and MEK pathway inhibitors in vitro and in mouse models of melanoma models. She found that BRAF inhibitors enhance or preserve T cell function in vitro and in vivo, whereas MEK inhibitors may compromise some aspects of T cell activation.	• Callahan MK, Masters G, et al. 2014. Paradoxical activation of T cells via augmented ERK signaling mediated by a RAF inhibitor. Can Immun Res 2(1):70-9.

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2011	Melanoma and Other Skin Cancers	Dr. Douglas Faller used a small molecule inhibitor of the signaling protein Protein Kinase Cδ (PKCδ) for specific targeting of melanoma with mutations in the NRAS gene and melanomas that have developed resistance to therapeutic inhibitors of BRAF. The PKCδ inhibitor lead compound has been refined for potency and specificity. Studies are ongoing to optimize a "final" compound that will be tested for clinical relevancy using a mouse melanoma model. Military Service members are at greater risk for the development of melanoma due to increased sun exposure.	• Chen Z, Forman LW, et al. 2014. Protein kinase C-δ inactivation inhibits the proliferation and survival of cancer stem cells in culture and in vivo. BMC Cancer 14:90-8. • Takashima A, English B, et al. 2014. Protein kinase Cδ is a therapeutic target in malignant melanoma with NRAS mutation. ACS Chem Biol 9(4):1003-14.
2011	Mesothelioma	Dr. Ravi Salgia targeted malignant pleural mesothelioma (MPM) with a trio of small molecule inhibitors that block three cellular signaling molecules: MET (also known as haptocyte growth factor receptor) receptor tyrosine kinase, phosphatidylinositol 3-kinase (PI3K), and mammalian target of rapamycin (mTOR). The combined use of these inhibitors was more effective than using any single drug in suppressing MPM cell motility and growth in vitro and tumor growth in an in vivo mesothelioma mouse model.	• Kanteti R, Dhanasingh I, et al. 2014. MET and PI3K/mTOR as a potential combinatorial therapeutic target in malignant pleural mesothelioma. PLoS One 9(9):e105919.
2011	Pancreatic Cancer	Dr. Robert Fletterick screened over 5 million compounds to find the first antagonists of liver receptor homolog 1 (LRH1), which 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.
2011	Pancreatic Cancer	Dr. David Yu identified CHD7 as a novel biomarker candidate for predicting gemcitabine response for early-stage resected pancreatic ductal adenocarcinoma patients, and he 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 33(47):5450-56.
2011	Pediatric Brain Cancer	Dr. Xiao-Nan Li used the seed money from a Concept Award to establish five new xenograft mouse models of diffuse intrinsic potine glioma (DIPG), a rare and lethal childhood brain tumor that occurs at the base of the brain. With these new cell lines, Dr. Li was able to create animal models of the DIPG for further studies.	• PRCRP Research Highlight • Grasso CS, Tang Y, et al. 2015. Functionally defined therapeutic targets in diffuse intrinsic pontine glioma. Nat Med 21(6):555-9.
2012	Blood Cancer	Dr. Charles Lin attempted to create the first comprehensive chromatin and transcriptional map of multiple myeloma (MM) in both cell lines and primary patient cells. Analysis revealed asymmetry in the distribution of chromatin co-activators clustered at enhancer regions that contain disproportionate levels of co-activators found near key oncogenes in MM.	• Chapuy B, McKeown MR, et al. 2013. Discovery and characterization of super-enhancer-associated dependencies in diffuse large B cell lymphoma. Cancer Cell 24(6):777-90. • Lin CY, Erkek S, et al. 2016. Active medulloblastoma enhancers reveal subgroup-specific cellular origins. Nature 530(7588):57-62.

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2012	Blood Cancer	Improved models of how multiple myeloma (MM) progresses in the bone marrow are urgently needed to facilitate the development of MM inhibitors. Dr. Michaela Reagan developed a novel cell culture model based on a silk-protein scaffold that better mimics tumor growth in the bone than traditional culture models. This new model was used to study how MM grows in a bone marrow-like environment and how MM impairs bone growth. She identified the first microRNA (miR), a short regulatory nucleic acid, abnormally expressed in bone cancer patients. Targeting this miR could lead to therapeutics that enhance bone healing to fight cancer-induced bone disease and potentially reduce tumor burden.	• Swami A, Reagan MR, et al. 2014. Engineered nanomedicine for myeloma and bone microenvironment targeting. Proc Natl Acad Sci U S A 111(28):10287-92. • Reagan MR, Mishima Y, et al. 2014. Investigating osteogenic differentiation in multiple myeloma using a novel 3D bone marrow niche model. Blood 124(22):3250-59.
2012	Colorectal Cancer	Utilizing a high-throughput 3D cell culture model of colorectal cancer (CRC), Dr. Daniel LaBarbera identified a new class of drugs derived from the giant barrel sponge that inhibit a key transcriptional pathway. Dr. LaBarbera filed a patent on the derivatives.	• Li L, Abraham AD, et al. 2014. An improved high yield total synthesis and cytotoxicity study of the marine alkaloid neoamphimedine: An ATP-competitive inhibitor of Topoisomerase IIα and potent anticancer agent. Mar Drugs 12(9):4833-50. • Li L1, Zhou Q, et al .2016. High-throughput imaging: Focusing in on drug discovery in 3D. Methods 96:97-102.
2012	Mesothelioma	Dr. Haining Yang filed two U.S. patents and published a paper in *Carcinogenesis* describing how patients with a germline mutation in BRCA1-associated protein-1 (BAP1) exhibit seven-fold improved long-term survival compared to patients with stochastic mutations.	• Baumann F, Flores E, et al. 2015. Mesothelioma patients with germline BAP1 mutations have 7-fold improved long-term survival. Carcinogenesis 36(1):76-81. • Napolitano A, Antoine DJ, et al. 2016. HMGB1 and its hyperacetylated isoform are sensitive and specific serum biomarkers to detect asbestos exposure and to identify mesothelioma patients. Clin Cancer Res 22(12):3087-96.