

## 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.	<ul style="list-style-type: none"> <li>Song BP, Jain S, et al. 2012. Detection of hypermethylated vimentin in urine of patients with colorectal cancer. <a href="#">J Mol Diagn</a> 14(2):112-19.</li> </ul>
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.	<ul style="list-style-type: none"> <li>Tilan J and Kitlinska J. 2010. Sympathetic neurotransmitters and tumor angiogenesis-link between stress and cancer progression. <a href="#">J Oncol</a> 539706.</li> </ul>
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.	<ul style="list-style-type: none"> <li>Feng Z, Liu L, et al. 2012. Chronic restraint stress attenuates p53 function and promotes tumorigenesis. <a href="#">Proc Natl Acad Sci USA</a> 109(18):7013-18.</li> </ul>
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.	<ul style="list-style-type: none"> <li>Gaziel-Sorvan A, Segura MF, et al. 2011. miRNA-30b/30d regulation of GAINAc transferase enhances invasion and immunosuppression during metastasis. <a href="#">Cancer Cell</a> 20(1):104-18.</li> </ul>
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.	<ul style="list-style-type: none"> <li>Nair T, Symanowski JT, and Gach HM. 2011. Comparison of complex permittivities of isotonic colloids containing single-wall carbon nanotubes of varying chirality. <a href="#">Bioelectromagnetics</a> 10.1002/bem 20689.</li> </ul>
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 gemcitabine as a candidate treatment that is progressing toward clinical trials.	<ul style="list-style-type: none"> <li><a href="#">PRCRP Research Highlight</a></li> <li>Tong Y, Merino D, et al. 2015. Cross-species genomics identifies TAF12, NFYC, and RAD54L as Choroid Plexus Carcinoma Oncogenes. <a href="#">Cancer Cell</a> 27(5): 712-27.</li> <li>Merino DM, Shlien A, et al. 2015. Molecular characterization of choroid plexus tumors reveals novel clinically relevant subgroups. <a href="#">Clin Cancer Res</a> 21(1): 184-92.</li> </ul>

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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.	<ul style="list-style-type: none"> <li>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. <a href="#">Mol Cancer Ther</a> 14(6); 1-9.</li> </ul>
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.	<ul style="list-style-type: none"> <li>Lu J, Ye X, et al. 2013. Endothelial cells promote the colorectal cancer stem cell phenotype through a soluble form of Jagged-1. <a href="#">Cancer Cell</a> 23(2):171-85.</li> </ul>
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.	<ul style="list-style-type: none"> <li>Anges, RS, Broome, et al. 2012. An optical probe for noninvasive molecular imaging of orthotopic brain tumors overexpressing epidermal growth factor receptor. <a href="#">Mol Cancer Ther</a> 11(10):2202-11.</li> </ul>
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.	<ul style="list-style-type: none"> <li>Gandra N and Singamaneni S. 2013. Surface-enhanced Raman scattering for in vivo imaging: The future looks BRIGHT? <a href="#">Nanomedicine</a> 8(3):317-20.</li> </ul>
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.	<ul style="list-style-type: none"> <li>Hindson CM, Chevillet JR, et al. 2013. Absolute quantification of low abundance targets by droplet digital PCR versus analog real-time PCR. <a href="#">Nat Methods</a> 10(10):1003-05.</li> </ul>
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.	<ul style="list-style-type: none"> <li>Kaplan FM, Kugel CH, et al. 2012. SHOC2 and CRAF mediate ERK1/2 reactivation in mutant NRAS-mediated resistance to RAF inhibitor. <a href="#">J Biol Chem</a> 287:41797-807.</li> </ul>
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.	<ul style="list-style-type: none"> <li>Knubel KH, Pernu BM, et al. 2014. MerTK inhibition is a novel therapeutic approach for glioblastoma multiforme. <a href="#">Oncotarget</a> 5(5):1338-1351.</li> <li>Pierce AM and Keating AK. 2014. TAM receptor tyrosine kinases: Expression, disease and oncogenesis in the central nervous system. <a href="#">Brain Res</a> 13:1542:206-220.</li> </ul>
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.	<ul style="list-style-type: none"> <li><a href="#">PRCRP Research Highlight</a></li> <li>Newman AM, Liu CL, et al. 2015. Robust enumeration of cell subsets from tissue expression profiles. <a href="#">Nat Methods</a> 12(5): 453-7.</li> </ul>

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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.	<ul style="list-style-type: none"> <li>• 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. <a href="#">Leukemia</a> 27(11):2177-86.</li> <li>• Wei Y, Dimicoli S, et al. 2013. Toll-like receptor alterations in myelodysplastic syndrome. <a href="#">Leukemia</a> 27(9):1832-40.</li> </ul>
2011	Colorectal Cancer	Dr. Mansour Mohamadzadeh found that a LTA-deficient <i>L. acidophilus</i> 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.	<ul style="list-style-type: none"> <li>• Khazaie K, Zadeh M, et al. 2012. Abating colon cancer polyposis by <i>Lactobacillus acidophilus</i> deficient in lipoteichoic acid. <a href="#">Proc Natl Acad Sci USA</a> 109(26):10462-67.</li> </ul>
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.	<ul style="list-style-type: none"> <li>• Callahan M, Masters G, et al. 2014. Paradoxical activation of T cells via augmented ERK signaling mediated by a RAF inhibitor. <a href="#">Can Immun Res</a> 2(1):70-79.</li> </ul>
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.	<ul style="list-style-type: none"> <li>• Benod C, Carlsson J, et al. 2013. Structure-based discovery of antagonists of nuclear receptor LRH1. <a href="#">J Biol Chem</a> 288(27):19830-44.</li> </ul>
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.	<ul style="list-style-type: none"> <li>• Colbert LE, Petrova AV, et al. 2014. CHD7 expression predicts survival outcomes in patients with resected pancreatic cancer. <a href="#">Cancer Res</a> 74(10):2677-87.</li> <li>• 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. <a href="#">Oncogene</a> 33(47):5450-56.</li> </ul>
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 pontine 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.	<ul style="list-style-type: none"> <li>• <a href="#">PRCRP Research Highlight</a></li> <li>• Grasso C, et al. 2015. Erratum: Functionally defined therapeutic targets in diffuse intrinsic pontine glioma. <a href="#">Nat Med</a> 4 May. 1-5.</li> </ul>
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.	<ul style="list-style-type: none"> <li>• Chapuy B, McKeown MR, et al. 2013. Discovery and characterization of super-enhancer-associated dependencies in diffuse large B cell lymphoma. <a href="#">Cancer Cell</a> 24(6):777-90.</li> </ul>

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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.	<ul style="list-style-type: none"> <li>Li L, Abraham A, et al. 2014. An improved high-yield total synthesis and cytotoxicity study of the marine alkaloid neoamphimedine: An ATP-competitive inhibitor of topoisomerasella and potent anticancer agent. <a href="#">Mar Drugs</a> 12(9):4833-4850.</li> </ul>
2012	Mesothelioma	Dr. Haining Yang filed two U.S. patents and published a paper in <a href="#">Carcinogenesis</a> 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.	<ul style="list-style-type: none"> <li>Baumann F, Flores E, et al. 2015. Mesothelioma patients with germline BAP1 mutations have 7-fold improved long-term survival. <a href="#">Carcinogenesis</a> 36(1):76-81.</li> </ul>