REPORT TO THE U.S. CONGRESS

U.S. ARMY MEDICAL RESEARCH AND MATERIEL COMMAND

CONGRESSIONALLY DIRECTED MEDICAL RESEARCH PROGRAMS

PEER REVIEWED CANCER RESEARCH PROGRAM

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Peer Reviewed Cancer Research Program
Report to Congress

TABLE OF CONTENTS

BACKGROUND and PURPOSE OF REPORT

The U.S. Army Medical Research and Materiel Command (USAMRMC) is a major subordinate Command of the U.S. Army Medical Command. The USAMRMC manages biomedical research and development programs that are part of the Department of Defense (DoD) and Army Science and Technology Master Plans. The Commanding General (CG), USAMRMC, is assigned authority as the Executive Agent for a number of medical research, development, and acquisition programs. Congressional appropriations totaling over $7 billion for fiscal years 1992 to 2012 (FY92-FY12) assigned to the USAMRMC are managed by the office of the Congressionally Directed Medical Research Programs (CDMRP), a subordinate organization within the USAMRMC. Biomedical research supported by these funds include research in autism spectrum disorder; breast, prostate, lung, ovarian, melanoma and genetic cancers; pediatric brain tumors, pediatric cancers, neurofibromatosis; tuberous sclerosis complex; Gulf War illness; and other research.

In additional efforts, the CDMRP works with the Joint Program Committees (JPCs) to execute a number of extramural programs. The combined effort leverages the CDMRP's expertise in research program administration with the JPCs' expertise in technical areas for the advancement of the mission to expedite the delivery of products and solutions that address challenges related to service members and their families. In FY12, the CDMRP assisted with program execution in the areas of neurotrauma, in-home and integrated mental health services, basic and applied psychological health, posttraumatic stress disorder (PTSD), traumatic brain injury (TBI), prosthetics, restoration of eye sight, and other conditions related to battlefield injury and military service.

As tasked to do so for program execution and management, the CDMRP is responsible for planning, coordinating, integrating, programming, budgeting, and executing the research programs. The CDMRP's flexible execution and management cycle includes the receipt of annual congressional appropriations, new research programs stakeholders meeting, vision setting, release of request for preproposals or proposals, preproposal screening and invitation to submit full applications, full application receipt and review, recommendation of grants for funding, and oversight of research grants.

Each program's advisory board (Integration Panel, Steering Committee, or JPC) of leading scientists, clinicians, military members, and/or disease survivors (consumers), recommends an investment strategy for the upcoming year that meets the unique needs of the research field, consumer community, and the military. The investment strategy is unique to each program and to each fiscal year cycle. By revisiting the investment strategy yearly, the program is able to explore innovative scientific ideas and research gaps spanning from basic laboratory science to clinical trials. Program announcements requesting research applications through specific award mechanisms are subsequently prepared and released.

The basic programmatic cycle for award recommendation is a two tiered system. To ensure that each program's research portfolio reflects not only the most meritorious science, but also the most programmatically relevant research, the CDMRP developed this two tiered model based upon recommendations from the Institute of Medicine (IOM) 1993 report.[1] The IOM

recommended a two step review procedure for research applications composed of a scientific peer review and a separate programmatic review. The scientific peer review is conducted by an external panel recruited specifically for each peer review session. It involves the expertise of scientists, clinicians, military members, and consumers. The peer review process includes evaluation of the applications based on a criterion process as delineated in the program announcements. Each application is judged on its own scientific and technical merit with respect to the described criteria. The second tier of review, the programmatic review, is conducted by the program's designated advisory panel, such as the Integration Panel for the Peer Reviewed Cancer Research Program (PRCRP). The Integration Panel for each program is charged with reviewing the applications based on the scientific peer review ratings, a balanced portfolio, programmatic intent, and relevance to the congressional language. Scientifically sound applications that best meet the program's interests and goals are recommended to the CG, USAMRMC, for funding. Once the CG approves the funding recommendations, awards are made in the form of one- to five-year grants, contracts, or cooperative agreements, and assigned to Science Officers for full-cycle support of research and outcomes. The programs that comprise the CDMRP are scientifically sound, innovative, and responsive to congressional intent and the needs of the public. The USAMRMC and the CDMRP have been praised by the IOM, which issued a report in 1997 stating it was favorably impressed with the processes implemented by the CDMRP and supported its continuation.[2]

In Public Law 110-329 from the Consolidated Security, Disaster Assistance, and Continuing Appropriations Act, 2009, a "peer-reviewed cancer research program" was appropriated for $16 million (M). In November 2008, the PRCRP was assigned to the USAMRMC, and subsequently to the CDMRP, for execution by the Assistant Secretary of Defense for Health Affairs, Force Health Protection. Public Law 111-118 from the 2010 Defense Appropriations Act directed funding of $15M. In April 2011, Public Law 112-10 from the Department of Defense and Full Year Continuing Appropriations Act directed $16M for the PRCRP. For the fiscal year 2012, Public Law 112-74 required a detailed status of the PRCRP, including research progress, accomplishments, and relevance to service members and their families, which was provided 21 February 2012. This report provides an update on the detailed status of the FY09-FY12 PRCRP cycle, research accomplishments, and the relevance of this type of research for U.S. military service members and their families.

FY09-FY12 PEER REVIEWED CANCER RESEARCH PROGRAM

Public Law 110-329 from the Consolidated Security, Disaster Assistance, and Continuing Appropriations Act, 2009, directed that $16M be appropriated for the FY09 PRCRP. The funds and directed research topic areas included $4M for melanoma and other skin cancers as related to deployments of service members to areas of high exposure; $2M for pediatric brain tumors within the field of childhood cancer research; $8M for genetic cancer and its relation to exposure to the various environments that are unique to a military lifestyle; and $2M for noninvasive cancer ablation treatment including selective targeting with nanoparticles. An inaugural stakeholders meeting was held on 23-24 February 2009 that included leading scientists, clinicians, military members, and consumers. Working groups from each topic area discussed gaps in scientific knowledge and research, consumer concerns, and military medicine. The

PRCRP Integration Panel was established in April 2009 to conduct vision setting to review the recommendations made at the stakeholders meeting, to craft a vision and mission of the program, and to develop an investment strategy. The vision of the FY09 PRCRP was to improve quality of life by significantly decreasing the impact of cancer on service members, their families, and the American public. To attain this goal, the FY09 PRCRP mission was to foster groundbreaking research, team science, and partnerships for the development of better prevention, earlier detection, and more effective treatments for cancer. Several program announcements were released in June 2009. Following the two levels of review, 38 awards across the four different topic areas were approved by the CG, USAMRMC.

In FY10, Public Law 111-118 from the 2010 Defense Appropriations Act directed funding of $15M for a "peer reviewed cancer research program" that would research cancers not addressed in the breast, prostate, lung, and ovarian cancer research programs currently executed by the DoD and, specifically, the USAMRMC. Specific topics included melanoma and other skin cancers, pediatric brain tumors within the field of childhood cancer research, genetic cancer research and genomic medicine, kidney cancer, blood cancer, colorectal cancer, *Listeria* vaccine for cancer, and radiation protection utilizing nanotechnology. An Integration Panel consisting of members of the FY09 PRCRP Integration Panel and new members to represent the congressional target areas was convened in March 2010. The Integration Panel recommended that the vision of the FY10 PRCRP remain unchanged from FY09, but that the mission be revised to read "to foster groundbreaking and collaborative research to accelerate progress in cancer prevention, detection, and therapeutic interventions." FY10 focus areas were defined for each topic area. Program announcements were released in May and June 2010. Relevance to military beneficiaries was required and reviewed at both peer and programmatic review. Following the two levels of review, 32 awards across the different topic areas were approved by the CG, USAMRMC.

For FY11, Public Law 112-10 from the Department of Defense and Full Year Continuing Appropriations Act directed $16M for the PRCRP. The Congressional Record of the Senate dated 14 December 2010 specified topics areas of melanoma and other skin cancers, pediatric cancer research, genetic cancer research, kidney cancer, blood cancer, colorectal cancer, pancreatic cancer, mesothelioma, *Listeria* vaccine for infectious disease and cancer, and radiation protection utilizing nanotechnology. This was later revised to remove *Listeria* vaccine for infectious disease. Further clarification acknowledged the requirement for relevance to service members and their families and that the funding would be directed toward research on cancers not addressed in the breast, prostate, lung (with the exception of mesothelioma), and ovarian cancer research programs currently executed by the DoD and, specifically, the USAMRMC. Vision setting was held on 19 April 2011. The FY11 Integration Panel consisting of members of the FY10 PRCRP Integration Panel and new members to represent the congressional target areas was convened to discuss research gaps, community needs, focus areas, and an investment strategy. Program announcements were released in June and September of 2011. Full application receipt was in October and November 2011. Peer review was in January 2012, followed by programmatic review in March 2012. The final recommendation for funding list of 43 awards was sent to the CG, USAMRMC and was approved.

For FY12, Public Law 112-74 directed $12.8M for the PRCRP. The committee provided funds directed to be used to conduct research in melanoma and other skin cancers, pediatric brain tumors, genetic cancer, pancreatic cancer, kidney cancer, blood cancer, colorectal cancer, mesothelioma, and *Listeria* vaccine for infectious disease and cancer. This was later revised to remove *Listeria* vaccine for infectious disease. The DoD has been directed to submit a report to the congressional defense committees on the status of the PRCRP, and, for each research area, include the funding amount awarded, the progress of research, and the relevance to service members and their families.

Vision setting for FY12 PRCRP was held in March 2012 with program announcements released in April 2012. Pre-application receipt was in June 2012. Pre-application screening was completed in July 2012. Application receipt was in September 2012 with peer review in November 2012 followed by programmatic review in January 2013, with award obligation no later than 30 September 2013.

FY13 PEER REVIEWED CANCER RESEARCH PROGRAM

The U.S. House of Representatives 112th Congress released the DoD Appropriations Bill Report for 2013 on 17 May 2012. Within the report, the committee directs $15 M for the PRCRP. This report provides funds to be directed for research into melanoma and other skin cancers, pediatric brain tumors, genetic cancer, pancreatic cancer, kidney cancer, blood cancers, colorectal cancer, mesothelioma and *Listeria* vaccine for infectious disease and cancer. The report requests the DoD to submit an update to the congressional defense committees on the status of the PRCRP, and, for each research area, include the funding amount awarded, the progress of research, and the relevance to service members and their families.

Vision setting for FY13 PRCRP was held in January 2013. Provided an appropriation to the DoD for the PRCRP for the FY13 cycle, program announcements will be released within 30 days of the DoD appropriations bill passage and signature by the President. Pre-application receipt will be 60 days following release of the program announcements. Pre-application screening should take place approximately 30 days later. Full application receipt should be scheduled approximately eight weeks or about 60 days following the invitation to submit. Peer review should be scheduled about eight weeks later followed by programmatic review at approximately 60 days later. Award obligation will be no later than 30 September 2014.

RESEARCH AREA INVESTMENT AND PROGRESS

For FY09 -FY11, all assistance agreements have been made and funds obligated to the institutions. Research area investment is detailed in Appendix A. Research areas included are blood cancer, colorectal cancer, genetic cancer (and genomic medicine), kidney cancer, *Listeria* vaccine for cancer, melanoma and other skin cancers, non-invasive cancer ablation, and pediatric brain tumor. In FY10, no applications in the research areas of radiation protection utilizing nanotechnology were recommended or selected for funding. Information for FY12 is presented in a Table II in Appendix A. These funds have not been obligated to the individual institution yet and are undergoing negotiations. Final awards are expected to be made no later than 30

September 2013. No awards in FY12 were recommended for *Listeria* vaccine for cancer because no full application was submitted.

A tabular summary of the proposed work and progress for each of the awards for FY09 and FY12 is contained in Appendix B. The log number, topic area, last name of principal investigator, award amount, institution, title, research progress, and military relevance are noted for each award. Awards for FY11 were obligated by 30 September 2012, and therefore investigations have just been initiated. Funding notifications has occurred for the FY12 cycle and award negotiations have started with a final obligation no later than 30 September 2013. Research will be initiated for FY12 according to the agreed upon start date, and the progress throughout the life cycle of the award will be monitored by Science Officers at the CDMRP.

RELEVANCE TO SERVICE MEMBERS and THEIR FAMILIES

The relevance of the PRCRP to service members and their families is determined by the impact of cancer on military service. Members of the military are exposed to hazardous environments and dangerous deployments due to the nature of their service and thus are at risk for the development of different types of cancers.[3] The Veterans Health Administration (VHA) identified malignancies that may be associated with military service (VHA-Directive 2003-34 Attachment B).

The Automated Central Tumor Registry of the DoD published data demonstrating that the incidence of melanoma was higher in the U.S. military population in comparison to the U.S. general population.[4] A meta-analysis using published epidemiological data on cancer risk in male military pilots, civilian pilots, and flight attendants revealed a higher standardized incidence ratio for melanoma and other skin cancers in those with exposure to specific physical, chemical, or biological factors (electromagnetic fields, jet fuel, volatile organic materials, etc.).[5] In addition, studies of common military exposures, such as aircraft maintenance, have been associated with an increased risk of cancer.[6] A recent study by Fastje et al[7] and funded by the PRCRP, showed that *in utero* exposure to tungsten and other environmental agents primed the immune system for aberrant responses to infectious agents and may lead to carcinogenic risk.

Yamane reported that the most frequent cancers diagnosed in Air Force service members between 1989 and 2002 were different from the general U.S. population, with a higher[8,9] incidence of melanoma, testicular, thyroid, cervical, and vulvar cancers in the Air Force population,[8]particularly cervical and vulvar cancer. Another review demonstrated a higher rate of prostate cancer in the military beneficiary population compared to the general population.[10] Occupational exposures is a frequent risk of military service. Asbestos related lung diseases such as mesothelioma is a known risk to Naval shipyard work[11]. It is generally accepted that nearly 95% of all mesothelioma cases are due to asbestos exposure.

Hodgkin's disease, a blood cancer, was the most common cancer diagnosis in men who served in the U.S. Navy.[12] The Selected Cancers Cooperative Study Group showed that veterans of the Vietnam War had a 50% increase in risk of Hodgkin's disease as compared to subjects who had not served in Vietnam.[13] Evidence links an increased risk for soft tissue sarcomas, non-Hodgkin's lymphoma, Hodgkin's disease, and chronic lymphocytic leukemia to Vietnam War

service and exposure to herbicides such as Agent Orange.[14] Cancer patterns of Vietnam War military women nurses in comparison to non-Vietnam War military women nurses and the general population showed that site-specific cancer patterns were different, with excess deaths from pancreatic and uterine corpus cancers in the Vietnam War military women nurses.[15] As the configuration of the military population changes to include more women, consideration into research on their risks and exposures is critical.

Two studies funded by the PRCRP recently published results which linked higher stress to increased cancer risk[16, 17]. Chronic stress murine models revealed an important link to attenuation of p53 (a tumor suppressor) and tumorigenesis[16]. Another study demonstrated the potent effect of neuropeptides and other stress mediators on tumor development and progression[17]. Stress and related issues are a concern of the military and the ultimate health and well-being of service members both during and after deployment.

Military families may also be at risk for developing cancers due to environmental exposures as shown by investigations into leukemia clusters near military aviation facilities.[18] Additionally, transgenerational occupational exposures may lead to increased risk of cancer development in progeny. Children of Vietnam War veterans have an increased risk of developing acute myeloid leukemia.[14] As shown by Hicks et al,[19] children of men in the Air Force had a higher incidence of tumors of the central nervous system (brain and spinal cord) and lymphatic system. The VHA acknowledged the toll of cancer on service members and their families when releasing its National Cancer Strategy in 2003 (VHA-Directive 2003-34). A serious illness in a family member, such as cancer, may have consequences on 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 a total of 355,442 military beneficiaries with a cancer diagnosis, for a prevalence of 4.1%, comprised of over 60 different cancer types.[20] The cost of cancer care within the Military Health System in FY02 was over $1 billion.[20] Funding studies on the detection, diagnosis, treatment, and prevention of these diseases benefits both the warfighter and the American public, ultimately leading to increased survival rates and decreased costs of medical care.

In summary, the CDMRP, USAMRMC, manages the FY09-FY13 PRCRP using its established and highly recognized management process. The FY13 PRCRP directly impacts military welfare by providing research into cancers that may develop due to exposure in various uniquely military environments. The CDMRP will plan, execute, and manage the FY09-FY13 PRCRP with the same rigor and integrity it has demonstrated for other research programs.

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APPENDIX A: TOTAL RESEARCH DOLLARS INVESTED PER TOPIC AREA

TABLE I: FISCAL YEAR 2009-2011 TOTAL DOLLARS INVESTED PER TOPIC AREA

Fiscal Year (FY) Topic Area Included[1]	Topic Area	Total Invested Dollars ($) FY09-FY11
2010-11	Blood Cancer	3,854,761
2010-11	Colorectal Cancer	3,299,173
2009-2011	Genetic Cancer[2]	10,073,383
2010-11	Kidney Cancer	2,312,990
2010-11	*Listeria* Vaccine for Cancer	839,200
2009-2011	Melanoma and Other Skin Cancers[3]	8,696,390
2011	Mesothelioma	1,188,720
2009	Non-invasive Cancer Ablation Therapy[4]	1,753,431
2011	Pancreatic Cancer	3,686,682
2011	Pediatric Cancers	1,024,660
2009-2010	Pediatric Brain Tumor	4,319,139
2010-11	Radiation Protection utilizing nanotechnology[5]	0
	Total Investment in Research Dollars[6]	41,048,529

[1]Designates the fiscal year of inclusion of the topic area in Congressional language.
[2]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.
[3]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.
[4]Non-invasive cancer ablation treatment including selective targeting with nanoparticles.
[5]No applications met the intention and scope of the program announcement for recommendation for funding.
[6]Total appropriation for FY09-FY11 was $47 million; total investment in research dollars is less USAMRMC and CDMRP management costs (~12.7%)

TABLE II: FY12 TOTAL DOLLARS INVESTED PER TOPIC AREA

Topic Area	Total Dollars Recommended[1] for Investment ($) FY12	Updated Total Invested FY09-FY12 ($)
Blood Cancer	3,063,475	6,918,236
Colorectal Cancer	2,856,317	6,155,490
Genetic Cancer	774,574	10,847,957
Kidney Cancer	746,160	3,059,150
Listeria Vaccine for Cancer	0[3]	839,200
Melanoma and Other Skin Cancers	1,218,000	9,914,390
Mesothelioma	636,270	1,824,990
Non-invasive cancer ablation[2]	0	1,753,431
Pancreatic Cancer	1,549,921	5,236,603
Pediatric Cancer[2]	0	1,024,660
Pediatric Brain Tumor	640,425	4,959,564
Radiation Protection utilizing nanotechnology[2]	0	0
Total Dollars for Investment[4]	**11,485,142**	**52,533,671**

[1] FY12 applications have been recommended for funding and are contingent upon funds availability and final award negotiations. FY12 appropriation was $12.8 Million.
[2] This topic area was not included in the FY12 Congressional language
[3] No full applications were submitted for this topic area
[4] Total appropriation for FY09-12 was $59.8 Million; total investment in research dollars is less USAMRMC and CDMRP management costs (12.2%)

APPENDIX B: FISCAL YEAR 2009 (FY09)-FY12 PEER REVIEWED CANCER RESEARCH PROGRAM RESEARCH LIST AND MILITARY RELEVANCE OF RESEARCH

Log Number/ Topic Area	Principal Investigator	Amount	Institution	Application Title	Research Project (RP) and Military Relevance (MR)
CA100164 Blood Cancer	Trobridge	$545,036	Washington State University, Pullman	Identification of Biomarkers for Myelodysplastic Syndrome (MDS) and Acute Myeloid Leukemia (AML) Using a Novel High-Throughput Forward Mutagenesis Screen	RP: Mutagenesis screen and drug development study for biomarkers of myelodysplastic syndrome (MDS) and acute myelogenous leukemia (AML). Generated transplanted mice for biomarker screening. MR: Military personnel are at risk of exposure to alkylating agents, in the form of chemical weapons, and ionizing radiation, from nuclear and/or radioactive sources that can cause therapy-related AML (t-AML)/ therapy-related MDS (t-MDS).
CA100254 Blood Cancer	Sarantopoulos	$443,899	University of North Carolina at Chapel Hill	BAFF-Driven Targeted Immunotherapy for Patients with Leukemia	RP: The long-term goal is to understand how BAFF (B-cell activating factor) promotes specific anti-leukemia responses, so novel therapeutic agents for leukemia can be developedEstablished 2 murine leukemia models for hematopoietic stem cell transplantation and vaccination treatment experiments. . MR: The environmental exposure to cytotoxins and chemicals during deployment is associated with higher incidence of leukemia.
CA100623 Blood Cancer	Lanza: Tomasson	$1,138,820	Washington University	Treatment of Multiple Myeloma with VLA4-Targeted Nanoparticles Delivering Novel c-MYC Inhibitor Prodrug	RP: Developments of novel Sn-2 prodrugs of c-Myc-Max inhibitors that are incorporated into lipid-encapsulated polysorbate-based nanoparticles. Ligands and prodrugs were synthesized and characterized. The cMyc Sn-2 prodrug had markedly improved bioactivity than the free drug in several myeloma cell types. The prodrug was highly retained in lipids. 3 manuscripts are under review, 2 new grants were submitted. MR: Multiple myeloma (MM) is a disease of particular relevance to our military veterans. Male veterans using Department of Veterans Affairs hospitals are at 51% increased risk of MM compared to the general public. Myc is an ideal target for anti-cancer therapeutics, but MM, which is particularly susceptible to disruption by interference in Myc-Max complexation, has thus far resisted attempts at targeted drug development.

Log Number/ Topic Area	Principal Investigator	Amount	Institution	Application Title	Research Project (RP) and Military Relevance (MR)
CA110020 Blood Cancer	Masamha	$250,662	University of Texas Health Science Center, Houston	Deciphering the Mechanism of Alternative Cleavage and Polyadenylation in Mantle Cell Lymphoma (MCL)	RP: Study to understand the mechanism of cyclin D1 mRNA alternative cleavage and polyadenylation as they pertain to aggressive Mantle Cell Lymphoma. MR: The environmental exposure to cytotoxins and chemicals during deployment is associated with a higher incidence of blood cancers.
CA110081 Blood Cancer	Newman	$376,790	Stanford University	Genomic Signatures for Integrative Models of Clinical Heterogeneity in Patients with Follicular Lymphoma	RP: Development of a novel method to determine which follicular lymphoma patients will be responsive to treatment. Research has just been initiated. MR: The environmental exposure to cytotoxins and chemicals during deployment is associated with a higher incidence of blood cancers.
CA110096 Blood Cancer	McClellan	$378000	Stanford University	Reprogramming of Human Acute Lymphoblastic Leukemia Cells by Myeloid Transdifferentiation	RP: Reprogram human B cell acute lymphoblastic leukemia (B-ALL) cells in vitro to characterize the genes involved in the process and to determine if it can be triggered in vivo and lead to disease regression. Research has just been initiated. MR: The environmental exposure to cytotoxins and chemicals during deployment is associated with a higher incidence of blood cancers.
CA110584 Blood Cancer	Reuther	$275,334	H. Lee Moffitt Cancer Center & Research Institute, at South Florida, University of	Enhancing Targeted Therapy for Myeloproliferative Neoplasms	RP: This study will focus on the molecular targeted therapy for myeloproliferative neoplasms and how it can be enhanced by combination therapy with modulators of lipid biosynthesis. Research has just been initiated. MR: The environmental exposure to cytotoxins and chemicals during deployment is associated with a higher incidence of blood cancers.

Log Number/ Topic Area	Principal Investigator	Amount	Institution	Application Title	Research Project (RP) and Military Relevance (MR)
CA110791 Blood Cancer	Wei	$315,922	M.D. Anderson Cancer Center, University of Texas	Innate Immunity Dysregulation in Myelodysplastic Syndromes	RP: Investigate whether a signaling axis is formed by Toll-like receptor activation of NF-kB, is maintained by the histone demethylase JMJD3, and is central to the pathogenesis of myelodysplastic syndromes (MDS). Research has just been initiated. MR: Military personnel are at risk of exposure to alkylating agents, in the form of chemical weapons, and ionizing radiation, from nuclear and/or radioactive sources that can cause therapy-related AML (t-AML)/ therapy-related MDS (t-MDS).
CA110834 Blood Cancer	FitzGerald	$200,000	National Cancer institute	Anti-CDR3 Therapy for B-Cell Malignancies	RP: Devise a proof of concept method for rapidly producing B-cell cancer specific immunotherapy molecules customizable to individual patients. Research has just been initiated. MR: The environmental exposure to cytotoxins and chemicals during deployment is associated with a higher incidence of blood cancers.
CA120025 Blood Cancer	Reagan	Under Negotiation	Dana-Farber Cancer Institute	Reciprocal Interactions between Multiple Myeloma Cells and Osteoprogenitor Cells Affect Bone Formation and Tumor Growth	RP: Determination the role of osteoprogenitor cells on the progression of multiple myeloma (MM) and elucidation of mechanisms by which MM cells alter their local bone microenvironment to encourage osteolysis. MR: Multiple myeloma (MM) is a disease of particular relevance to our military veterans. Male veterans using Department of Veterans Affairs' hospitals are at 51% increased risk of MM compared to the general public. This study will lead to novel targets for MM growth with bone.
CA120064 Blood Cancer	Brander	Under Negotiation	Duke University	Understanding Drug Resistance to Targeted Therapeutics in Malignant B-Cell Lymphoproliferative Disorders	RP: The study aims to determine mechanisms for drug resistance in chronic lymphocytic leukemia (CLL) and to define the role of the microenvironment in drug resistance to targeted small molecule inhibitors. MR: This study will potentially advance the care of military patients with leukemia.

Log Number/ Topic Area	Principal Investigator	Amount	Institution	Application Title	Research Project (RP) and Military Relevance (MR)
CA120120 Blood Cancer	Xie	Under Negotiation	Rutgers, New Jersey, State University of	Regulation of Mitochondria Function by TRAF3 in B Lymphocytes and B-Cell Malignancies	RP: Study the role of mitochondria in TRAF3 induced apoptosis in B cells. TRAF3 is novel tumor suppressor in B lymphocytes. TRAF3 deletions and mutations occur in a variety of B cell malignancies. The projected was recommended for funding recently. MR: This study will lead new avenues for the prevention and treatment of major blood cancers, which impacted many military personnel.
CA120128 Blood Cancer	Halene	Under Negotiation	Yale University	Assessing the Mechanisms of MDS and Its Transformation to Leukemia in a Novel Humanized Mouse	RP: Development of a humanized mouse model for MDS and study of the kinetics of progression of MDS to leukemia in vivo. MR: Myelodysplasia and leukemia affect military personnel with normal aging or with exposure to genotoxic agents. The proposed humanized MDS model will provide a unique platform to advance new therapeutics for these diseases.
CA120184 Blood Cancer	Lin	Under Negotiation	Dana-Farber Cancer Institute	Understanding Selective Downregulation of c-Myc Expression through Inhibition of General Transcription Regulators in Multiple Myeloma	RP: Investigation of the selectivity of JQ1 in multiple myeloma (MM). JQ1 is a small moleculr BET bromodomain inhibitor that serves as a therapeutic target for MM. The projected was recommended for funding recently. MR: Multiple myeloma (MM) is a disease of particular relevance to our military veterans. Male veterans using Department of Veterans Affairs' hospitals are at 51% increased risk of MM compared to the general public. This study will improve blood cancer treatment and benefit the military personnel with MM. ,
CA120212 Blood Cancer	Cheloufi	Under Negotiation	Massachusetts General Hospital	Investigating Epigenetic Parallels between Carcinogenesis and Reprogramming to Pluripotency	RP: Identification of the epigenetic regulators of somatic cell reprogramming to pluripotent stem cells and characterization of the common molecular traits of cancer cells and induced pluripotent stem cells. MR: The study has broad impact in the understanding of cancer development and identification of novel cancer drug targets, which will lead to a better quality of life of the service members and their families.

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CA120373 Blood Cancer	Liu	Under Negotiation	Indiana University, Indianapolis	Modulating Leukemia-Initiating Cell Quiescence to Improve Leukemia Treatment	RP: Determination of the role of necdin in the initiation of acute myelogenous leukemia (AML) and characterization of whether lowering of necdin expression affects the response of leukemia initiating cells to chemotherapy or radiotherapy. MR: This study will lead to the understanding the necidin functions in normal and leukemic stem cells, which will lead to innovative clinical applications in eradicating leukemia-initiating cells and benefit those impacted by the disease in military personnel.
CA120381 Blood Cancer	Reshef	Under Negotiation	Pennsylvania, University of	Chemokine Receptor Signatures in Allogeneic Stem Cell Transplantation	RP: To determine the role of chemokine receptor expression in regulating the organ distribution of effector T cells after stem cell transplantation and to determine the effect of targeted chemokine receptor blockade on trafficking patterns of T-cell clones. MR: Graft-versus-host disease is a major cause of morbidity and mortality in allogeneic stem cell transplantation (SCT). This study can improve the outcomes of allogeneic SCT in treatment of blood cancers.
CA100111 Colorectal Cancer	Jessup	$313,725	National Cancer Institute	Inhibition of Embryonic Genes to Control Colorectal Cancer Metastasis	RP: Investigation into the embryonic genes, primarily Nanog and SOX2, on regulation of the development of metastases in colorectal cancer (CRCDemonstrated NANOGP8 can rescue stemness in CRC. *Oncogene* (2012), 1-9. MR: CRC is the second highest cause of cancer-specific mortality in the general public and military population. Approximately 50% of military personnel and dependents who are diagnosed with colon or rectal carcinoma will die of the disease.
CA100512 Colorectal Cancer	Eckhardt: Tan	$505,443	University of Colorado Denver	Collaborative Model for Acceleration of Individualized Therapy of Colon Cancer	RP: This research relates directly to the thematic area of CRC to advance progress in the treatment of the disease using predictive biomarkers and novel preclinical modelsCompleted screening for 6 anti-cancer agents on CRC cells; Data being analyzed. MR: The largest segment of the military, white males, has an incidence rate of 53/100,000, whereas black males have a higher incidence (and mortality) of 63/100,000. Only about 50% of CRC patients are completely cured by surgery, thus recurrent and metastatic disease is an ongoing problem.

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CA100879 Colorectal Cancer	Ellis	$592,307	University of Texas M. D. Anderson Cancer Center	Microenvironmental Influence of Endothelial Cells on Colorectal Cancer Stem Cell Phenotype	RP: Study into the complex reactions of inflammation, endothelial cells, and cancer stem cells for the development of chemoresistance. Preliminary results indicated that endothelial cell secreted factors are involved in promoting and maintaining cancer cell stemness in CRC, which contributed to chemoresistance in CRC. MR: The understanding of critical pathways to resistance will support military cancer treatment of service members and their families.
CA110130 Colorectal Cancer	Yue	$364,800	Notre Dame, University of	Proteomic Analysis to Identify Functional Molecules in Drug Resistance Caused by E-Cadherin Knockdown in 3D-Cultured Colorectal Cancer Models	RP: Conduct a proteomic analysis to identify functional molecules in drug resistance caused by E-cadherin knock-down in 3D cultured colorectal cancer models. Research has just been initiated. MR: CRC is the second highest cause of cancer-specific mortality in the general public and military population. Approximately 50% of military personnel and dependents who are diagnosed with colon or rectal carcinoma will die of the disease.
CA110261 Colorectal Cancer	Potts	$318000	Texas, University of, Southwestern Medical Center at Dallas	Role of Germline MAGE Cancer-Testis Antigens in Colorectal Cancer	RP: Investigate the role of MAGE cancer-testis antigens as oncogenes driving cell transformation and tumorigenesis in colorectal cancer. Research has just been initiated. MR: CRC is the second highest cause of cancer-specific mortality in the general public and military population. Approximately 50% of military personnel and dependents who are diagnosed with colon or rectal carcinoma will die of the disease.
CA110495 Colorectal Cancer	Kufe	$341,040	Dana-Farber Cancer Institute	Targeting of the MUC1-C Oncoprotein in Colitis-Associated Colorectal Cancer	RP: To exlopre the mechanisms responsible for the progression of inflammatory bowel disease to colorectal cancer to discover new strategies for drug development. Research has just been initiated. MR: CRC is the second highest cause of cancer-specific mortality in the general public and military population. Approximately 50% of military personnel and dependents who are diagnosed with colon or rectal carcinoma will die of the disease.
CA111002 Colorectal Cancer	Mohamadzadeh	$293000	University of Florida	Reprogramming Intestinal Immunity by Novel L. Acidophilus Strains Results in Protective Immunity against	RP: to elucidate the regulartory effects of L. acidophilus surface layer proteins on induced intestinal inflammation and to demonstrate the regulatory effects of L. acidophilus SlpA in decreasing cancer-promoting inflammation in colonic polyposis. Research has just been intiated. MR: CRC is the second highest cause of cancer-specific mortality in

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				Colon Cancer	the general public and military population. Approximately 50% of military personnel and dependents who are diagnosed with colon or rectal carcinoma will die of the disease.
CA120050 Colorectal Cancer	Laederich	Under Negotiation	University of California at San Diego	Modulating Multireceptor Network in Invasive Colorectal Cancers via a Single Interface	RP: To characterize and modulate the effect of blocking the interface between the receptor and G-protein on CRC using GIV-biosensor. MR: This study will provide a novel approach to treat CRC and can potentially reduce the mortality of military personnel with CRC.
CA120053 Colorectal Cancer	Williams	Under Negotiation	University of Houston	Elucidate the Estrogen Receptor Beta Mechanism for Colon Cancer Prevention and Treatment	RP: Study the role of estrogen receptor β on NFkB regulation, inflammation and colon cancer inhibition. MR: This study will advance both basic and translational research for the benefit of military beneficiaries and others with colon cancer.
CA120296 Colorectal Cancer	Kizhakke Mattada	Under Negotiation	University of Virginia	Functional Characterization of CENP-A Post-Translational Modifications in Chromosome Segregation	RP: Study the mechanism of centromeric protein A (CENP-A) methylation and its role in chromosome segregation and cancer development. MR: CRC is the second leading cause of cancer death in US. This study could potential lead to new target for CRC treatment and reduce cancer burden among military beneficiaries.
CA120403 Colorectal Cancer	Shah	Under Negotiation	University of Michigan, Ann Arbor	The Role of the Noncanonical NF-KappaB Pathway in Colon Cancer	RP: Determine the role of Akt1 and Akt2 in the induction, invasiveness and metastatic potential of CRC and determine the role of Akt -isoform-dependent phosphorylation events in CRC progression. MR: This study will identify new targets for the development of therapeutics for CRC, which could benefit military personnel impacted by CRC.
CA120261 Colorectal Cancer	LaBarbera	Under Negotiation	University of Colorado Denver - Anschutz Medical Campus	Novel Antimetastatic Agents for the Treatment of Drug-Resistant and Metastatic Colon Cancer	RP: Development of new competitive ATPase inhibitor of topoisomerase IIa that blocks t-cell transcription factor (TCF) transcription and inhibits the metastasis of CRC. MR: Active military personnel, veterans, and family members are at considerable risk for CRC. Novel therapies that target TCF-transcription may prevent metastasis and recurrence of CRC.

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CA120206 Colorectal Cancer	MacNeill	Under Negotiation	Wake Forest University Health Sciences	Electrically Conducting Polymer Nanoparticles to Selectively Target and Treat Metastatic Colorectal Cancer	RP: Development of near-infrared phototherapy using electrical conducting polymer nanoparticles to treat colorectal cancer. MR: This new polymer-based nanomaterials hold promise to selectively target and treat CRC and benefit military personnel impacted by CRC.
CA120342 Colorectal Cancer	Sebastian	Under Negotiation	Massachusetts General Hospital	Role of SIRT6 in Metabolic Reprogramming During Colorectal Carcinoma	RP: Study the role of SIRT6 in regulating glycolytic activity and transformation in CRC cells and determine the role of SIRT6 in CRC development. MR: Understanding the metabolic reprogramming in CRC can offer an alternative way for therapeutic development and benefit the military personnel impacted by CRC.
CA093054 Genetic Cancer	Lantz	$113,319	University of Arizona, Tucson	The Carcinogenic Potential of JP-8 and Tungsten in C57BL/6 Mice	RP: Study of environmental exposures (JP-8 and tungsten) known to be a risk for service members and their interactions with viral infections, which may lead to long-term health consequences such as cancer development. The study found that JP-8 alone did not cause reactivation of Epstein-Barr virus (MHV-68). Yet the combination of utero exposure to tungsten and other environmental agents was able to prime the immune system for aberrant response to infectious agents. Publication: *Chem Biol Interact*. 2012 Apr 5;196(3):89-95. MR: Military personnel encounter environmental exposures related to their service that risk long-term health care issues, e.g., leukemia clusters
CA093111 Genetic Cancer	Yennu-Nanda	$115,500	University of Texas M. D. Anderson Cancer Center	Role of Melanin in Oncogenesis	RP: Results showed the induction of excessive melanin production leads to changes in gene expression profiles dependent on skin type. MR: The prevention and early diagnosis modalities will be of immense benefit to U.S. soldiers on the frontlines.

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CA093139 Genetic Cancer	Cao	$559,548	Clemson University	New Protein Modification under Nitrosative Stress	RP: Reactive nitrogen species leads to unstable DNA and carcinogenesis. In progress. Treatment of endonuclease V with NO donors resulted in decreased DNA repair activity. The reduced activity of NO-treated endonuclease V could be rescued by thioredoxin. Publication: *J Biol Chem* (2011) 285:41483-41490. *Nucleic Acids Res (2011)* 39:536-544. MR: Explosions and blasts occurring in battlefield operations intensify the contacts of military personnel with gaseous reactive nitrogen species and may inflict acute and chronic impact on the health of military personnel. - Military activities increase risks of nitrogen species exposures.
CA093155 Genetic Cancer	Wallis-Schultz	$109,875	Texas A&M University	Functional Genomics Screen for Radiation Responsive Genes in Mutant Mouse Embryonic Stem Cells	RP: Identification of candidate genes responsible for cellular response to radiation exposure. This project involved the search for genes that affect the cellular response to radiation exposure and led to the identification and validation of seven differentially expressed candidate genes. MR: Armed forces members are occupationally at higher risk for exposure to carcinogenic radiation sources such as excessive sunlight and depleted uranium. Military exposures and risks include radiation exposures, which have long-term health risk factors and outcomes.
CA093176 Genetic Cancer	Su	$111,301	Drexel University	Development of a Genetic Urine Test Using a Padlock-Mediated Microarray for Colon Cancer Screening	RP: Development of colorectal cancer biomarker test using urine. Outcomes: (2012) *J Mol Diagn*14(2):112-9. MR: Technological advances supported by the military increase the ability of military medicine to answer the needs of service members and their families and decrease general health care costs to the military.
CA093193 Genetic Cancer	Elble	$109,125	Southern Illinois University	A Novel Therapy for Metastatic Melanoma	RP: Study of the CLCA2 tumor suppressor gene therapy methodology in prevention and treatment of melanoma. Demonstrated that restoration of CLCA2 expression is lethal to melanoma cells. MR: Deployment to areas of high ultraviolet (UV) exposures puts service members at increased risk for the development of melanoma and other skin cancers.

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CA093204 Genetic Cancer	Yusuf	$109,399	University of Alabama at Birmingham	Role of p16/INK4a in Ultraviolet Radiation-Induced Inflammation and Photocarcinogenesis	RP: Study the role of p16 in UVB radiation induced inflammation and skin tumor development. Outcome: One manuscript to be submitted. MR: Deployment to areas of high UV exposures puts service members at increased risk for the development of melanoma and other skin cancers.
CA093257 Genetic Cancer	Chen	$96,750	Southern California Institute for Research and Education	Monitor microRNA Expression in Blood and Saliva to Detect Radiation-Induced Cancer Progression	RP: Development of a blood and/or saliva biomarker test for radiation-induced lymphomas. MR: Military personnel are at higher risk of radiation exposures related to their service and therefore development of long-term health issues such as lymphomas and leukemias.
CA093269 Genetic Cancer	Ongkeko	$115,875	University of California, San Diego	Tobacco and Nicotine Promote Acquisition of Cancer Stem Cell Properties in Head and Neck Cancer	RP: Study of the impact of nicotine and smoking on cancer stem cell. . Outcome: (2012*) Plos ONE* 7(12): e51967. doi:10.1371/journal.pone.0051967 MR: Military personnel have high level of cigarette smoking than the general population. Nicotine and tobacco smoking is a risk factor for head and neck cancer.
CA093337 Genetic Cancer	Kitlinska	$114,500	Georgetown University	Neuropeptide Y: A New Link between Stress and Cancer	RP: Examination of the role of chronic exposure to psychological and physical stress on cancer progression via release of neuropeptide Y. Potent effects of neuropeptide Y and other stress mediators on tumor development and progression has been demonstrated. Outcomes: (2010) *J. Oncology* 2010: 1-6. MR: Understanding the role of post-traumatic stress disorder and chronic stress in potential future cancer development of veterans is an important area of research.
CA093377 Genetic Cancer	Armani	$383,315	University of Southern California	Real-Time Detection of DNA Methylation	RP: Development of a new tool to detect epigenetic changes in response to environmental factors that the service members encounter. The PI reported progresses on sensor design, instrument design and surface chemistry of labeling. *Applied Physics Letters* (2012), 100, 013305. MR: Radiation exposure is of high risk in military populations.

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CA093395 Genetic Cancer	Brooks	$560,148	Maine Medical Center	UV-Induced Triggering of a Biomechanical Initiation Switch within Collagen Promotes Development of a Melanoma-Permissive Microenvironment in the Skin	RP: Study of the mechanism of UV radiation damage and melanoma and other skin cancers. The study showed that UV radiation of extracellular matrix (ECM) proteins altered the adhesion, migration and proliferation of fibroblast, melanoma cells and macrophages in vitro; UV exposure of mouse skin induced inflammation and exposure of the HU177 cryptic collagen epitope. MR: Deployment to areas of high UV exposures puts service members at increased risk for the development of melanoma and other skin cancers.
CA093415 Genetic Cancer	Hu	$428,999	University of Medicine and Dentistry of New Jersey, Robert Wood Johnson Medical School	Psychological Stress Promotes Irradiation-Induced Tumorigenesis through Attenuation of p53 Function	RP: Study of the linkage between chronic stress, radiation exposure, and cancer development. This study provided a direct link between chronic stress and tumorigenesis in mouse models, and revealed the attenuation of p53 function as an important underlying mechanism by which chronic stress promotes tumorigenesis. Publication: *PNAS*, (2012) 109, 7013-7018. MR: Understanding the role of chronic stress and radiation exposure for potential future cancer development in the veteran population is of significant military relevance.
CA093417 Genetic Cancer	Yusuf	$404,299	University of Alabama at Birmingham	Regulation of Ultraviolet Radiation-Induced Cutaneous Photodamage and Nucleotide Excision Repair by Toll-Like Receptor-4	RP: Study of the gene expression and linkages to UV radiation damage. The study found that Toll-like Receptor 4(TLR4) deficiency enhanced DNA repair in mouse skin after UVB exposure; cytokine IL-2 had a significant effect on repairing cyclobutane pytimidine dimmers (CPD) in TLR4 knockout mice. MR: Deployment to areas of high UV exposures puts service members at increased risk for the development of melanoma and other skin cancers.

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CA093422 Genetic Cancer	Jimeno	$404,849	University of Colorado Denver	The XactMice: A Xenochimaeric Mouse with Tumor and Hematopoietic System Obtained from the Same Patient	RP: Development of mouse model to better understand carcinogenesis and its treatment. The study demonstrated the feasibility of engrafting human tumors on humanized mice. MR: Advancing genetic research has a direct application to active, reserve, and retired U.S. service members and their families, since military lifestyle entails potential exposure to carcinogens known and presumed, chemical and physical/radioactive in nature. both in training and in deployment, and related to equipment utilization and/or combat.
CA093492 Genetic Cancer	Testa	$657,517	Fox Chase Cancer Center	Role of the Inflammasome in Asbestos-Induced Mesothelioma Formation	RP: Study of the role of NALP3 inflammsome and the development of mesothelioma due to asbestos exposure. Preliminary data suggested that blocking inflammasome-mediated IL-1β processing and release during asbestos exposure might be a venue for treating mesothelioma. MR: Asbestos exposure was widespread among naval personnel even after the 1980s. Malignant mesothelioma has a long lag time of 20-40 years from the initial exposure to the diagnosis of the disease. Long-term risk of mesothelioma development following asbestos exposures is critical for U.S. veterans and active military.
CA093544 Genetic Cancer	Cantor	$653,132	Children's Hospital, Boston	Runx-1-Centered Transcriptional Pathways as Tools to Discover Novel Genetic Risk Factors for Radiation-Induced Myelodysplastic Syndrome and Leukemia	RP: Characterization of a potential gene target (Runx1) of chemical and radiation exposures that may lead to cancer development. This study identified 5'UTR mutations in ANKRD26 gene as a novel cause of leukemia predisposition and thrombocytopenia in humans. This award led to a new grant application. MR: Advancing genetic research has a direct application to active, reserve, and retired U.S. military personnel and their families, as a military lifestyle entails potential exposure to carcinogens known and presumed, chemical and physical/radioactive in nature, both in training and in deployment, and related to equipment utilization and/or combat.
CA093566 Genetic Cancer	Dai	$423,038	Oregon Health & Science University	Regulation of c-Myc mRNA by L11 in Response to UV and Gamma Irradiation	RP: Study of the downregulation of key gene (c-myc) due to DNA damage. The study indicated that miRNA mediated c-myc mRNA decay is an important mechanism for ribosomal biogenesis and c-Myc activity during stress conditions. *Mol Cell Biol* (2011) 31:4007 MR: Exposure to environmental hazards in military personnel is associated with increased cancer risks. Studies of hazardous exposures that may causes damage to DNA and long-term health care issues such as cancer will be beneficial to military personnel.

Log Number/ Topic Area	Principal Investigator	Amount	Institution	Application Title	Research Project (RP) and Military Relevance (MR)
CA093573 Genetic Cancer	Majeti	$449,979	Stanford University	Genetic Characterization of Leukemia Stem Cells in Chemical- and Radiation-Induced Acute Myelogenous Leukemia	RP: Identification and molecular characterization of leukemia stem cells (LSC) from mouse models of t-AML/t-MDS induced by alkylating agents or ionizing radiation. The study established a mouse model of radiation-induced t-AML/t-MDS; a mouse model of alkylator-induced t-AML/t-MDS. Pre-leukemic bone marrow samples were collected for further analysis. MR: Military personnel are at risk of exposure to alkylating agents, in the form of chemical weapons, and ionizing radiation, from nuclear and/or radioactive sources that can cause t-AML)/t-MDS.
CA093588 Genetic Cancer	Tsao	$631,258	Massachusetts General Hospital	Governance of Cutaneous Photocarcinogenesis by Chronic UVA-Exposed Dermal Fibroblasts	RP: Investigation of the impact of UVA in skin cancer development. The study created a co-culture system and demonstrated that UVA irradiation increased oxidative stress in fibroblasts, and confirmed a bystander transmission of reactive oxygen species from the fibroblast target to neighboring not irradiated cells. MR: Melanoma and other skin cancers represent a significant disease burden to U.S. military. Military is at risk for higher UV radiation exposures and melanoma development and other skin cancers.
CA093616 Genetic Cancer	Kemp	$659,431	Fred Hutchinson Cancer Research Center	Transgenerational Radiation Epigenetics	RP: Study to identify an epigenetic signature of radiation exposure in normal lung tissue and determine if these epigenetic changes are also seen in radiation-induced lung tumorsTissues from animals with and without irradiation were collected. Data analysis was under the way. MR: Military at risk for radiation exposures (UV and gamma) and development of cancers.
CA100459 Genetic Cancer	Moritz; Foltz	$1,204,447	Institute for Systems Biology: Swedish Health Services	Development of Advanced Technologies for Complete Genomic and Proteomic Characterization of Quantized Human Tumor Cells	RP: Study of three innovative new tools (single-cell analysis of human glioblastomas, complete genome sequencing of two families each containing an individual with glioblastoma, and complete genome sequencing of 10 cells from each quantized single-cell determined population and targeted mass spectrometry of the glioblastoma tumors) to find relevant biomarkers for novel approaches to the study of all cancers. Progress was made in technical development of whole genome sequencing and quantitative assays for human proteins. MR: Technological advances supported by the military increase the ability of military medicine to answer the needs of service members and their families.

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CA100545 Genetic Cancer	Broome	$571,946	Medical University of South Carolina	Targeting Cancer Protein Profiles with Split-Enzyme Reporter Fragments to Achieve Chemical Resolution for Molecular Imaging	RP: Study to advance imaging technology toward chemical resolution at the single cell level. NIRF-EGF peptide probe was synthesized; genetically engineered rat glioma cell lines with 0, 1, and 2 human receptors were created. MR: This platform holds promise of imaging cancers with greater specificity and providing a clearer linkage between pathologically indistinguishable cancer stages. Technological advances supported by the military increase the ability of military medicine to answer the needs of service members and their families.
CA100865 Genetic Cancer	Alvarez: Couto: Huang	$855,142	Research Institute at Nationwide Children's Hospital: Ohio State University	Integrative Lifecourse and Genetic Analysis of Military Working Dogs	RP: Identification of environmental influences with potential to alter gene structure, stability, and expression, thereby altering cancer risk. Identification of specific genetic variations and environmental exposures, resulting in different epigenetic profiles capable of modifying cancer risk. The informatics infra-structure, statistical method for analyzing genetic data, database have been established. MR: The study of military working dogs, environmental exposures, and cancer risk will directly relate to military exposures and cancer risk within the human handlers population.
CA120109 Genetic Cancer	Wignall	Under Negotiation	Northwestern University	Targeting Centrosome-Clustering Mechanisms to Selectively Kill Cancer Cells	RP: To identify proteins required for centrosome clustering in human cancer cells. Centrosome is unique to cancer cells during the cell division. The identified proteins could be unique targets for blocking cancer cell division. MR: Technological advances supported by the military increase the ability of military medicine to answer the needs of service members and their families.
CA120215 Genetic Cancer	Gutierrez	Under Negotiation	Children's Hospital, Boston	Zebrafish Functional Genetics Approach to the Pathogenesis of Well-Differentiated Liposarcoma	RP: To examine oncogenes that contributes to well-differentiated lipsarcoma in a zebra fish model. MR: Past exposure to herbicidal agents used in the Vietnam War and to radiation predispose to the soft-tissue sarcomas. Development of effective therapies for sarcoma will benefit to military servicemen and veterans.

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CA100587 Kidney Cancer	Singamaneni	$454,900	Washington University	Label-Free, Point-of-Service Assay for Noninvasive Detection of Kidney Cancer	RP: Study to develop a urine test for kidney cancer. The study demonstrated a 3D surface enhanced Raman scattering (SERS) substrate was 2 orders of magnitude more sensitive compared to planar 2D substrate; it also demonstrated the detection limit of AQP1, a urinary biomarker for kidney cancer, at 10 ng/ml. A novel biosensig platform in the form of bioplasmonic paper was created with a capability of 20ng/ml sensitivity*Nano Lett.* (2012) 12, 2645; 2); *Chem Comm* (2012) 48, 1677; 3); *Nanotechnology* (2012) 23, 255502; 4);*Nanosci Lett* (2012) 2, 10; 5); *Mater Chem* (2011) 21, 15218; 6) ; *Nanoengineering and nanomanufacturing* (2011), 1, 113. MR: Successful development of such a test will enable early cancer detection, removal at a curative and kidney-sparing stage, prompt recovery, and earlier return to active duty.
CA100606 Kidney Cancer	Tewari: Pantuck	$1,245,727	Fred Hutchinson Cancer Research Center: University of California, Los Angeles	Early Diagnosis of Clear Cell Kidney Cancer via VHL/HIF Pathway-Regulated Circulating microRNA	RP: Development of a serum miRNA-based biomarker for early detection of kidney cancer. The study optimized the detection method for miR-210 and demonstrated that miR-210 was elevated in renal carcinoma serum samples. MR: Successful development of such a test will enable early cancer detection, removal at a curative and kidney-sparing stage, prompt recovery, and earlier return to active duty.

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CA101070 Kidney Cancer	Wang	$115,869	University of California, San Francisco	Noninvasive Assessment of Renal Tumor Aggressiveness Using Hyperpolarized 13C MR	RP: Development of imaging tools (MRI [magnetic resonance imaging]) to discriminate between indolent and aggressive renal cancers (RC). The study demonstrated the feasibility of using 13C pyruvate magnetic resonance to differentiate metastatic RC from localized RC. (2013) *Cancer Res* 73(2) 529–38. MR: This work is of potential significant impact on military beneficiaries because of (1) the higher incidence of renal cell carcinoma in men versus women (2:1 ratio), (2) the risk of cigarette smoking (doubles the risk of renal cell carcinoma), and (3) the risk of occupational exposure to heavy metals, chlorinated solvents, and petrochemicals. Successful development of such a test will enable early cancer detection, removal at a curative and kidney-sparing stage, prompt recovery, and earlier return to active duty.
CA110032 Kidney Cancer	Sriram	$240,000	California, University of, San Francisco	Hyperpolarized ^{13}C MR Markers of Renal Tumor Aggressiveness	RP: To test a new technique of hyperpolarized carbon-13 magnetic resonance to determine if it can differentiate between benign and aggressive kidney tumors. Research has just been initiated. MR: This work is of potential significant impact on military beneficiaries because of (1) the higher incidence of renal cell carcinoma in men versus women (2:1 ratio), (2) the risk of cigarette smoking (doubles the risk of renal cell carcinoma), and (3) the risk of occupational exposure to heavy metals, chlorinated solvents, and petrochemicals. Successful development of such a test will enable early cancer detection, removal at a curative and kidney-sparing stage, prompt recovery, and earlier return to active duty.
CA110769 Kidney Cancer	Frisch	$296,000	West Virginia University	Role of Grainyhead in Kidney Cancer	RP: the study of Grainyhead, a transcription factor involved in kidney development, to determine it's role as a tumor suppressor for renal cell carncinoma and how it prevents RCC progression. Research has just been initiated. MR: This work is of potential significant impact on military beneficiaries because of (1) the higher incidence of renal cell carcinoma in men versus women (2:1 ratio), (2) the risk of cigarette smoking (doubles the risk of renal cell carcinoma), and (3) the risk of occupational exposure to heavy metals, chlorinated solvents, and petrochemicals. Successful development of such a test will enable early cancer detection, removal at a curative and kidney-sparing stage, prompt recovery, and earlier return to active duty

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CA120297 Kidney Cancer	Krishnan	Under Negotiation	University of North Carolina at Chapel Hill	Reprogramming of the Kinome to Enhance Mammalian Target of Rapamycin (mTOR) Inhibitor Responsiveness in Renal Cell Carcinoma	RP: To identify kinases upregulated by mammalian target of rapamycin (mTOR) inhibitors in renal cancer cell and to determine if inhibition to these kinase improves the responsiveness of mTOR inhibitors in renal cell carcinoma. MR: This study could potentially improve the outcomes and survival of military personnel with RCC.
CA120409 Kidney Cancer	Shen	Under Negotiation	Health Research, Inc., Roswell Park Division	A Novel Tumor Antigen and Foxp3 Dual-Targeting Tumor Cell Vaccine Enhances the Immunotherapy in a Murine Model of Renal Cell Carcinoma	RP: Characterization of the biological activity and therapeutic potential of a novel tumor cell antigen and Foxp3 dual-targeting vaccine as a single treatment or in combination with tasquinimod in a RCC mouse model. MR: Service members have higher risk to develop kidney cancer because of deployment related exposure to environment hazards.
CA100463 Listeria Vaccine for cancer	Chung	$543,200	Memorial Sloan-Kettering Cancer Center	Evaluation of Immune Responses Mediated by *Listeria*-Stimulated Human Dendritic Cells: Implications for Cancer Vaccine Therapy	RP: Development of *Listeria* modulated human dendritic cells (DC) for enhanced immunoresponse for cancer vaccination. The study demonstrated that Listeria induced DC maturation and activation, which subsequently stimulated T cell proliferation. These findings confirmed that Listeria could stimulate immune response and could potentially serve as a DC vaccine adjuvant. MR: The development of immune enhanced technology will benefit military medicine from cancer to infectious diseases (a main exposure risk in deployed military populations).
CA110297 Listeria Vaccine for cancer	Bahjat	$296,000	Providence Portland Medical Center	Synergy of SOCS-1 Inhibition and Microbial-Based Cancer Vaccines	RP: To test the hypothesis that the induction of negative regulators of inflammation and cytokine signaling, such as SOCS-1, limit the potency of the tumor-specific immune response and that the inhibition of SOCS-1 will enhance the anti-tumor efficacy of a Listeria monocytogenes-based cancer vaccine. Research has just been initiated. MR: The development of immune enhanced technology will benefit miliary medicine from cancer to infectious diseases (a main exposure risk in deployed miliary populations).

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CA093370 Melanoma/Skin Cancer only	Kashani-Sabet; Leachman	$1,188,381	California Pacific Medical Center: University of Utah	Molecular Determinants of Melanoma Susceptibility and Progression	RP: Development of a melanoma risk prediction model in the U.S. military population. Preparation for sample analysis was completed. Permission of accessing the DoD ACTUR database was obtained. The query to the database was submitted. MR: Deployment to areas of high UV exposures puts service members at increased risk for the development of melanoma and other skin cancers. Study directly relates to military population and risk.
CA093471 Melanoma/Skin Cancer only	Hernando: Osman	$1,187,984	New York University School of Medicine	Altered microRNAs in Melanoma Brain Metastasis	RP: Characterization of the metastasis potential of melanomas. In progress. The study found that melanoma brain metastasis associated miRNAs contributed to the adaptation of melanoma cells to the brain parenchyma. *Cancer Cell*(2011) 20(1):104-118; *Cancer* (2011) 117(8):1711-1720. MR: The prevention, detection, and treatment of melanoma are of particular importance to the military population, who are at high risk due to the deployment related exposure to UV radiation.
CA093473 Melanoma/Skin Cancer only	Halaban: Brash: Bosenberg	$1,196,001	Yale University	UVL, ROS, Pigmentation, Genetic Predisposition, and Epigenetic Gene Silencing in Melanoma	RP: Study of the linkage between reactive oxygen species (ROS), genetic and epigenetic changes, and UV radiation leading to melanoma development. The study found a "photochemistry in the dark" phenomena, which is that DNA damage by UV light continued after sun exposure. The delayed sunlight damage could be prevented by an identified agent. This finding could lead to a new formulation of sunscreen to protect the delayed skin damage by sun exposure. MR: The prevention, detection, and treatment of melanoma are of particular importance to the military population, who are at high risk due to the deployment-related exposure to UV radiation.
CA100039 Melanoma and other skin cancers	Antony	$561,626	University of Maryland, Baltimore	Mechanisms of Relapsing Cancer and the Origin of Melanoma-Specific Regulatory T Cells	RP: Study of immunosuppression and melanoma development. The study found a more complexed role of T_{reg} cells in melanoma relapse. Removing T_{reg} cells did not prevent or treat melanoma relapse. MR: The high exposure to UV radiation to the military personnel during military deployment is associated with increased risk for melanoma. Learning how immunosuppression works may lead to therapies for controlling autoimmune diseases as well such diseases such as arthritis and diabetes, which also affect military personnel and their families.

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CA100311 Melanoma and other skin cancers	Aplin	$581,250	Jefferson Medical College	Role and Regulation of FOXD3 in Mutant B-RAF Melanoma	RP: This study aims to understand resistance mechanisms in melanoma in order to provide the basis for improved targeted therapeutic strategies. The study established systems to analyze the response of melanoma xenografts to RAF inhibitors in vivo. MR: The prevention, detection, and treatment of melanoma are of particular importance to the military population, who are at high risk due to the deployment related exposure to UV radiation.
CA101019 Melanoma and other skin cancers	Aplin	$116,250	Jefferson Medical College	Novel Mechanisms of Resistance to B-RAF Inhibitors in Melanoma	RP: Study into the novel mechanisms of chemotherapy resistance to RAF inhibitors and melanoma treatments. A system has been developed to quantify changes in ERK1/2 signaling in tumor cells with elevated activity, which is important as ERK1/2 reactivation can lead to relapse in BRAF treated patients. (2012) *J Biol Chem* 287:41797-41807. MR: The rate of new melanoma diagnoses among service members is higher than that of the general population even after correcting for age and ethnicity. Melanoma is strikingly the second most common cancer among males in the U.S. Navy. Military is at risk for UV radiation exposures and development of cancers.
CA101118 Melanoma and other skin cancers	Serafini	$114,750	University of Miami School of Medicine	Converting Myeloid-Derived Suppressor Cells into Immunogenic Antigen-Presenting Cells in Melanoma-Bearing Mice	RP: Investigation of the conversion of the tolerogenic myeloid-derived suppressor cells by siRNA into functional immunogenic activated protein C to generate effective tumor immunity. Confimration that genetic modification via shRNA of tumor educated myeloid cells is sufficient to alter the immune system by creating an anti-tumor immune response able to restrain the growth of melanomas.MR: Service members are deployed to areas of high risk and exposure to UV light. With more and more deployment of troops in countries with high sun exposure and UVA and UVB penetration (e.g., Afghanistan, Iraq, and the Middle East region), melanoma can be the most frequent cancer that military personnel will face during their lives.

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CA101202 Melanoma and other skin cancers	Libermann	$130,500	Beth Israel Deaconess Medical Center, Boston	Testing New Drugs for Treatment of Melanoma Patients Applying Connectivity Map Database Analysis with Melanoma Gene Signatures	RP: Technology-driven study to map the treatment and disease to exploit the chemotherapeutic properties of drugs. MR: Military at risk for UV radiation exposures and development of cancers.
CA110011 Melanoma and other skin cancers	Ransom	$240,000	Colorado, University of, at Denver	Determining the Location of DNA Modification and Mutation Caused by UVB Light in Skin Cancer	RP: To map and characterize UVB damaged "hotspots" in the human genome using a novel enzyme and sequencing methodology. Research has just been initiated. MR: Service members are deployed to areas of high risk and exposure to UV light. With more and more deployment of troops in countries with high sun exposure and UVA and UVB penetration (e.g., Afghanistan, Iraq, and the Middle East region), melanoma can be the most frequent cancer that military personnel will face during their lives.
CA110017 Melanoma and other skin cancers	Goding	$368,400	Maryland, University of, Baltimore	Therapeutic Intervention for the Treatment of Relapsing Melanoma	RP: To determine the roles of chronic CD4 T cell exhaustion and the inhibitory pathways involved in melanoma tumor relapse. Research has just been initiated. MR: The rate of new melanoma diagnoses among service members is higher than that of the general population even after correcting for age and ethnicity. Melanoma is strikingly the second most common cancer among males in the U.S. Navy. Military is at risk for UV radiation exposures and development of cancers.
CA110094 Melanoma and other skin cancers	Callahan	$322,849	Memorial Sloan-Kettering Cancer Center	Evaluation of the Immunologic Impact of RAF Inhibitors to Guide Optimal Combination of RAF Inhibitors and Immunotherapy for the Treatment of Advanced Melanoma	RP: To investigate ways to optimally combine targeted pathway inhibition with checkpoint blockade to develop strategies that lead to the control of melanoma. Research has just been initiated. MR: Service members are deployed to areas of high risk and exposure to UV light. With more and more deployment of troops in countries with high sun exposure and UVA and UVB penetration (e.g., Afghanistan, Iraq, and the Middle East region), melanoma can be the most frequent cancer that military personnel will face during their lives.

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CA110107 Melanoma and other skin cancers	Zhang	$259,200	Mount Sinai School of Medicine, New York	Insight into Skin Tumorigenesis Highlighting the Function of Epigenetic Regulators in SCC Formation	RP: To dissect the Ezh2 regulatory network that controls sSCC formation, focusing on the evaluation of regulatory networks and their mechanisms in control of the early steps of sSCC formation. Research has just been initiated. MR: Service members are deployed to areas of high risk and exposure to UV light. With more and more deployment of troops in countries with high sun exposure and UVA and UVB penetration (e.g., Afghanistan, Iraq, and the Middle East region), melanoma can be the most frequent cancer that military personnel will face during their lives.
CA110183 Melanoma and other skin cancers	Marchetti	$313,000	Baylor College of Medicine	Heparanase Mechanisms in Melanoma Brain Metastasis	RP: To examine the use of heparanase as a novel therapeutic target for the personalized treatment of melanoma brain metastasis. Research has just been initiated. MR: The rate of new melanoma diagnoses among service members is higher than that of the general population even after correcting for age and ethnicity. Melanoma is strikingly the second most common cancer among males in the U.S. Navy. Military is at risk for UV radiation exposures and development of cancers.
CA110338 Melanoma and other skin cancers	Bikle	$296,400	Northern California Institute for Research and Education	The Tumor Suppressor Actions of the Vitamin D Receptor in Skin	RP: In vivo study of the vitamin D receptor as a tumor suppressor in relation to epidermal tumor formation through the blocking of the beta catenin and hedgehog pathways. Research has just been initiated. MR: The rate of new melanoma diagnoses among service members is higher than that of the general population even after correcting for age and ethnicity. Melanoma is strikingly the second most common cancer among males in the U.S. Navy. Military is at risk for UV radiation exposures and development of cancers.
CA110396 Melanoma and other skin cancers	Faller	$327,333	Boston University Medical Campus	Targeting N-Ras as a Therapeutic Approach for Melanoma	RP: To test whether the inhibition or down-regulation of PKCsigma in human and murine models of melanoma with aberrant activation of N-RAS signaling will cause targeted cytotoxicity in melanoma tumors. Research has just been initiated. MR: Service members are deployed to areas of high risk and exposure to UV light. With more and more deployment of troops in countries with high sun exposure and UVA and UVB penetration (e.g., Afghanistan, Iraq, and the Middle East region), melanoma can be the

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					most frequent cancer that military personnel will face during their lives.
CA110462 Melanoma and other skin cancers	Zhang	$289,871	Colorado, University of, Denver, Anschutz Medical Campus	Targeting "Dynamic Stemness" of Melanoma by Blocking the NADH-Dependent CtBP Function	RP: study whether hypoxia, hyperglycemia, and UV irradiation trigger the conversion of melanoma cells by the activation of CtBP-mediated transcription and if blocking it's function can be used as a novel therapeutic strategy. Research has just been initiated. MR: Military at risk for UV radiation exposures and development of cancers.
CA110602 Melanoma and other skin cancers	Hernando	$284,597	New York University School of Medicine	Identification of Glycomic Alterations during Melanoma Metastasis	RP: To determine if keratinocyte stem cells are chemotactic and migrate away from the skin and into the bone marrow. Research has just been initiated. MR: Deployment to areas of high UV exposures puts service members at increased risk for the development of melanoma and other skin cancers. Study directly relates to military population and risk.
CA110802 Melanoma and other skin cancers	Morris	$305,000	Minnesota, University of, Twin Cities	A Novel Mechanism for the Pathogenesis of Nonmelanoma Skin Cancer Resulting from Early Exposure to Ultraviolet Light	RP: To determine if keratinocyte stem cells are chemotactic and migrate away from the skin and into the bone marrow. Research has just been initiated. MR: The rate of new melanoma diagnoses among service members is higher than that of the general population even after correcting for age and ethnicity. Melanoma is strikingly the second most common cancer among males in the U.S. Navy. Military is at risk for UV radiation exposures and development of cancers.
CA110823 Melanoma and other skin cancers	Bullock	$308,000	Virginia, University of	Functional Proteomics to Identify Moderators of CD8+ T-Cell Function in Melanoma	RP: To identify and characterize inhibitory molecules expressed by melanoma tumor infiltrating CD8+ cells through the novel use of functional proteomics incorporating phage display. Research has just been initiated. MR: Military at risk for UV radiation exposures and development of cancers.

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CA111032 Melanoma and other skin cancers	Basu	$305,000	Ohio State University	Role of Catecholamines in the Regulation of Angiogenesis in Preneoplastic Skin Lesions	RP: To investigate the role of dopamine receptors during skin carcinogenesis and to elucidate the molecular mechanisms by which these receptors regulate vascular endothelial growth factor A in the skin. Research has just been initiated. MR: Service members are deployed to areas of high risk and exposure to UV light. With more and more deployment of troops in countries with high sun exposure and UVA and UVB penetration (e.g., Afghanistan, Iraq, and the Middle East region), melanoma can be the most frequent cancer that military personnel will face during their lives.
CA120099 Melanoma and other skin cancers	Ceol	Under Negotiation	Massachusetts, University of, Medical School	Uncovering the Role of BMP Signaling in Melanocyte Development and Melanoma Tumorigenesis	RP: Investigation of the bone morphogenetic protein GDF6 in melanocyte development and melanoma tumorigenesis MR: Melanoma is one of the most common cancers among active-duty personnel. This study could serve as a diagnostic and prognostic marker of melanoma.
CA120161 Melanoma and other skin cancers	Wu	Under Negotation	Massachusetts General Hospital	Targeting Palmitoyl Acyltransferases in Mutant NRAS-Driven Melanoma	RP: Development of a new class of palmitoyl acyltransferase (PAT) inhibitors that target N-RAS mutant melanomas. MR: Deployment to areas of high UV exposures puts service members at increased risk for the development of melanoma and other skin cancers. This study will lead to new therapeutics to combat melanoma, which can improve the survival and quaulify of life of the impacted personnel.
CA120240 Melanoma and other skin cancers	Yan	Under Negotiation	Yale University	Targeting Epigenetic Regulator JARID1B in Malignant Melanoma	RP: Determination of the effects of an epigenetic regulator, JARID1B loss on melanoma formation and progression in the Braf/Cdkn2a mouse melanoma model. MR: The military service members are at increased risk for melanoma and other skin cancers. This study aims to identify novel inhibitors to a drug target for melanoma. The outcome could be translated into novel clinical application for the treatment of melanoma.

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CA110442 Mesothelioma	Robinson	$296,850	Western Australia, University of	Targeting Immunological Restrainers: Understanding the Immunology Behind Combination Chemoimmunotherapy to Improve the Treatment of Malignant Mesothelioma	RP: To determine if the adaptive immune response plays a key role in the early changes associated with mesothelial cell trasformation and tumor development and is inhibited by immunological restraints. Research has just been initiated. MR: Asbestos exposure was widespread among naval personnel even after the 1980s. Malignant mesothelioma has a long lag time of 20-40 years from the initial exposure to the diagnosis of the disease. Long-term risk of mesothelioma development following asbestos exposures is critical for U.S. veterans and active military.
CA110751 Mesothelioma	Sharma	$308,000	California, University of, Los Angeles, David Geffen School of Medicine	Mesothelioma Snail-Mediated Modulation of Inflammatory Responses	RP: To determine if mesothelioma Snail knockdown will have an impact on tumor growth, invasion and migration by modulating the activities of immune effectors and suppressors. Research has just been initiated. MR: Asbestos exposure was widespread among naval personnel even after the 1980s. Malignant mesothelioma has a long lag time of 20-40 years from the initial exposure to the diagnosis of the disease. Long-term risk of mesothelioma development following asbestos exposures is critical for U.S. veterans and active military.
CA110765 Mesothelioma	Salgia	$316,000	Chicago, University of	PI3K as a Therapeutic Target in Malignant Pleural Mesothelioma	RP: To investigate the therapeutic potential of phosphatidyl inositol 3'-kinase (PI3K) in Malignant Pleural Mesothelioma and determine the efficacy of some of the PI3K and PI3K/TOR inhibitors in MPM cell culture and mouse models. Research has just been initiated. MR: Asbestos exposure was widespread among naval personnel even after the 1980s. Malignant mesothelioma has a long lag time of 20-40 years from the initial exposure to the diagnosis of the disease. Long-term risk of mesothelioma development following asbestos exposures is critical for U.S. veterans and active military.
CA110772 Mesothelioma	Heasley	$294,870	Colorado, University of, Denver, Anschutz Medical Campus	Targeting Fibroblast Growth Factor Receptor Signaling Pathways in Mesothelioma	RP: To test the hypothesis that the co-expression of fibroblast growth factors (FGFs) and FGF Receptors create an autocrine growth loop in mesotheliomal that promotes cancer growth. Research has just been initiated. MR: Asbestos exposure was widespread among naval personnel even after the 1980s. Malignant mesothelioma has a long lag time of 20-40 years from the initial exposure to the diagnosis of the disease. Long-

Log Number/ Topic Area	Principal Investigator	Amount	Institution	Application Title	Research Project (RP) and Military Relevance (MR)
					term risk of mesothelioma development following asbestos exposures is critical for U.S. veterans and active military.
CA120102 Mesothelioma	Klein	Under Negotiation	VA Medical Center, Minneapolis, MN	Development of Novel p16INK4a Mimetics as Anticancer Therapy	RP: Determination of the structure-function relationships of overlapping peptides derived from p16INK4a that inhibit the activity of CDK4/6; screening stabilized peptides that inhibit CDK4/6; and preclinical assessment of the stabilized peptides. MR: Mesothelioma is a highly fatal disease that can affect those exposed to asbestos, especially those who have been in Navy ships and shipbuilding. This study could lead to targeted therapy with reduced side effects and higher efficacy.
CA120355 Mesothelioma	Yang	Under Negotiation	Hawaii, University of	Mesothelioma: Identification of the Key Molecular Events Triggered by BAP1	RP: Study the impact of BAP1 on the release of HMGB1 and other downstream factors; and the effect of BAP1 status on the development of mesothelioma. MR: Veterans from all branches of the armed forces are at high risk for mesothelioma due to the widespread use of asbestos in the construction of military vehicles, air craft, ships, and buildings. To understand the pathways activated by HMGB1 in the development of mesothelioma could potentially lead to better diagnosis and treatment of mesothelioma.
CA093108 Non-invasive Ablation only	O'Donnell	$114,836	University of California, Davis	Immuno-Nanomicelles Targeted Therapy of Non-Hodgkin's Lymphoma	RP. Research into fabrication and development of nanomicelles for the direct delivery of treatment (chemotherapy) to disease site (non-Hodgkins lymphoma).. Mice treated with these encapsulated micelles had a superior anti-tumor effect as compared to using vincristine alone. Outcomes: (2012) *Mol Pharm* 9(6): 1727-1735. MR: Biomedical development of nanotechnology that is translatable to various treatments for diseases, conditions, and injuries specific to the military deployments and exposure risks, e.g., Agent Orange.

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CA093166 Non-invasive Ablation only	Gach	$134,884	Nevada Cancer Institute	Targeted RF Ablation of Tumors Using Monocyte/ Macrophage Carriers of Conductive Nanoparticles	RP: Development of radiofrequency (RF) ablation therapies for specific treatment of tumors. Preliminary data indicate that metallic single-wall carbon nanotubes may have the potential to generate enough heat at biologically relevant concentrations to have an impact in clinical use. (2012) *Bioelectromagnetics* 33:134-146. MR: Development of a new treatment modality for tumor ablation may translate to expansive medical methodologies with military benefit.
CA093180 Non-invasive Ablation only	Berdis	$117,684	Case Western Reserve University	Gold-Containing Nucleosides as Noninvasive Ablation Agents	RP: Development of gold-containing nucleosides as target agents to potentiate the efficacy of ionizing radiation for maximal tumor ablation. Invention disclosure submitted to the Technology Transfer office at Case Western Reserve University. (2012*) J Med Chem*55(5):2437-51. MR: Technological advances supported by the military increase the ability of military medicine to answer the needs of service members and their families.
CA093210 Non-invasive Ablation only	Pan	$117,000	Chicago, University of	Testing Delivery Platforms for New Anticancer tRNA-Based Drugs	RP: Development of killer tRNA nanoparticles as blood cancer treatment. MR: The military benefits through the development of drug delivery systems to decrease side effects and increase efficacy. Technology can be broadly employed for various treatments outside cancer.
CA093389 Non-invasive Ablation only	Torti	$598,307	University of Connecticut	Targeted Nanoparticles for Kidney Cancer Therapy	RP: Development of novel optically activated multifunctional nanotubes to target and kill renal cancer cells. Soluble D5-conjugated nanotubes were produced; the toxicity of unconjugated nanotubes to kidney cancer cells was tested. The results demonstrated that the combination of NIR and nanotubes could successfully inhibited both human and mouse kidney cancer cells. MR: Biomedical development of nanotechnology that is translatable to various treatments for diseases, conditions, and injuries specific to the military will benefit military personnel.

Log Number/ Topic Area	Principal Investigator	Amount	Institution	Application Title	Research Project (RP) and Military Relevance (MR)
CA093453 Nonvasive Ablation only	Panyam	$670,720	University of Minnesota, Twin Cities	Targeted Magnetic Hyperthermia for Lung Cancer	RP: Development of super-paramagnetic iron oxide nanoparticles to specifically target lung tumor cells Outcomes: The study demonstrated that super paramagnetic iron oxide nanoparticles (SPIO NPs) with EGFR targeting ligand enhanced tumor cell uptake and in vivo mouse lung retention. MR: Military biomedical development of nanotechnology that is translatable to various treatments for diseases, conditions, and injuries specific to the military will benefit military personnel.

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CA110164 Pancreatic cancer	Lunt	$368,400	Michigan State University	Understanding the Warburg Effect and the Metabolic Requirements of Cancer Cells	RP: To uncover the metabolic pathways that blood and pancreatic cancers rely on for survival that are not used by normal cells as these pathways could be used as targets for new therapies. Research has just been initiated. MR: Higher risk of pancreatic cancer has been shown in populations exposed to pesticides such as Agent Orange. Higher risk of pancreatic cancer in Vietnam nurses has been reported.
CA110164 Pancreatic cancer	Houchen	$296,000	Oklahoma, University of, Health Sciences Center	Tuft Cell Regulation of miRNAs in Pancreatic Cancer	RP: To test the hypothesis that tuft cells are specialized chemosensing cells in the pancreas and upon appropriate oncogenic signals become the cells of origin for pancreatic cancer. Research has just been initiated. MR: Higher risk of pancreatic cancer has been shown in populations exposed to pesticides such as Agent Orange. Higher risk of pancreatic cancer in Vietnam nurses has been reported.
CA110449 Pancreatic cancer	Beatty	$320,000	Pennsylvania, University of	Listeria Vaccines for Pancreatic Cancer	RP: Examination of whether Listeria vaccines can overcome the immune suppression associated with pancreatic ductal adenocarcinoma by stimulating anti-tumor responses able to target both tumor cells and their surrounding microenviroment. Research has just been initiated. MR: Higher risk of pancreatic cancer has been shown in populations exposed to pesticides such as Agent Orange. Higher risk of pancreatic cancer in Vietnam nurses has been reported.
CA110530 Pancreatic cancer	Solomon	$241,880	National Cancer Institute	Metabolomic Profiles and Pancreatic Cancer Risk	RP: the study of metabolites to identify those associated with pancreatic cancer to define profiles correlating with risk levels. Research has just been initiated. MR: Higher risk of pancreatic cancer has been shown in populations exposed to environmental agents and pesticides such as Agent Orange. Higher risk of pancreatic cancer in Vietnam nurses has been reported.
CA110535 Pancreatic cancer	Yu	$310,000	Emory University	The Replication Stress Response in Pancreatic Cancer	RP: to identify Replication Stress Response genes and evaluate them as potential biomarkers for pancreatic cancer treatment response. Research has just been initiated. MR: Higher risk of pancreatic cancer has been shown in populations exposed to environmental agents and pesticides such as Agent Orange. Higher risk of pancreatic cancer in Vietnam nurses has been reported.

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CA110636 Pancreatic cancer	Fletterick	$313,690	California, University of, San Francisco	Inhibition of Pancreatic Cancer Cell Proliferation by LRH-1 Inhibitors	RP: To find selective and potent compounds that inhibit LRH-1 activity in human pancratic ductal adenocarcinoma cells and therefore blunt their growth, proliferation, and spread. Research has just been initiated. MR: Higher risk of pancreatic cancer has been shown in populations exposed to environmental agents and pesticides such as Agent Orange.
CA110724 Pancreatic cancer	Phanstiel	$289,988	Central Florida, University of	Development of Novel Cancer Therapies that Target Polyamine Metabolism	RP: To determine if sustatined polyamine depletion in human pancreatic cells leads to apoptosis so that a combination therapy can be developed using inhibitors of polyamine biosynthesis and transport. Research has just been initiated. MR: Higher risk of pancreatic cancer has been shown in populations exposed to environmental agents and pesticides such as Agent Orange. Higher risk of pancreatic cancer in Vietnam nurses has been reported.
CA110731 Pancreatic cancer	Corcoran	$340,894	Massachusetts General Hospital	An in Vivo shRNA-Drug Screen to Identify Novel Targeted Therapy Combinations for KRAS Mutant Cancers	RP: To use a novel in vivo RNAi drug screening approach to rapidly identify genes that when in inhibited, allow MEK inhibitors to work against KRAS mutant pancreatic cancer cells. Research has just been initiated. MR: Higher risk of pancreatic cancer has been shown in populations exposed to environmental agents and pesticides such as Agent Orange. Higher risk of pancreatic cancer in Vietnam nurses has been reported.
CA110832 Pancreatic cancer	Mukherjee	$290,720	North Carolina, University of, at Charlotte	A Novel Association and Therapeutic Targeting of Neuropilin-1 and MUC1 in Pancreatic Cancer	RP: To exploration of the hypothesis that MUC1, a marker of aggressive tumors, is driving metastatic spread by increasing Neurophilin 1 levels within pancreatic tumors. Research has just been initiated. MR: Higher risk of pancreatic cancer has been shown in populations exposed to environmental agents and pesticides such as Agent Orange.
CA110994 Pancreatic cancer	Sabatini	$388,633	Whitehead Institute for Biomedical Research	Targeting Pathways that Process Endogenous Toxic Metabolites in Pancreatic Cancers	RP: To identify the pathways that produce and remove endogenous toxic metabolites in pancreatic cancers and to examine how those pathways can be targeted to selectively cause toxicity in pancreatic cancer cells. Research has just been initiated. MR: Higher risk of pancreatic cancer has been shown in populations exposed to environmental agents and pesticides such as Agent Orange. Higher risk of pancreatic cancer in Vietnam nurses has been reported.

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CA111019 Pancreatic cancer	Jacks	$311,152	Massachusetts Institute of Technology	Investigating the Mechanism of K-RAS-Independent Growth of Murine Pancreatic Ductal Adenocarcinoma in Vitro and in Vivo	RP: To use RNAi-based technology to knockdown K-RAS mutant cells both in vivo and in vitro to identify the K-RAS independent growth pathways in pancreatic cancer that can be targeted for drug therapy. Research has just been initiated. MR: Higher risk of pancreatic cancer has been shown in populations exposed to environmental agents and pesticides such as Agent Orange. Higher risk of pancreatic cancer in Vietnam nurses has been reported
CA111036 Pancreatic cancer	Kimmelman	$215,325	Dana-Farber Cancer Institute	In Vivo Measurement of Oncogenic Kras-Dependent Glucose Metabolism in Mouse Models of Pancreatic Cancer	RP: To develop a novel method to measure the incorporation of glucose into pancreatic tumor models to assess where it is metabolized to develop a list of critical elevated metabolites and their associated pathways. Research has just been initiated. MR: Higher risk of pancreatic cancer has been shown in populations exposed to environmental agents and pesticides such as Agent Orange. Higher risk of pancreatic cancer in Vietnam nurses has been reported
CA120188 Pancreatic Cancer	Rhim	Under Negotiation	University of Pennsylvania	A Novel Mechanism for Post-Transcriptional Regulation in Pancreatic Cancer Progression	RP: Study the RNA-DNA differences (RDD) in pancreatic pre-cancer and tumor cells and determine the genes in which RDD occur during cancer progress. MR: Pancreatic cancer is one of the most lethal forms of cancer that affects service members, veterans and military beneficiaries and their family.
CA120057 Pancreatic Cancer	Ting	Under Negotiation	Massachusetts General Hospital	Impact of Noncoding Satellite Repeats on Pancreatic Cancer Metastasis	RP: Study the role of RNA satellites in pancreatic cancer genetics, metastasis and circulating tumor cells. MR: Higher risk of pancreatic cancer has been shown in populations exposed to environmental agents and pesticides such as Agent Orange. Higher risk of pancreatic cancer in Vietnam nurses has been reported
CA120412 Pancreatic Cancer	Nagrath	Under Negotiation	University of Michigan, Ann Arbor	Integrated Microfluidic Magnetic CTC Sorter and Enumerator for Early Diagnosis and Management of Pancreatic Cancer	RP: Development of an integrated microfluid magnetic cell sorter and enumerator to separate circulating tumor cells (CTC) from blood for early diagnosis of pancreatic cancer. MR: Higher risk of pancreatic cancer has been shown in populations exposed to environmental agents and pesticides such as Agent Orange. Higher risk of pancreatic cancer in Vietnam nurses has been reported.

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CA120028 Pancreatic Cancer	Du	Under Negotiation	Cornell University, Weill Medical College	RHAMMB Promotes Liver-Specific Metastasis of Pancreatic Neuroendocrine Tumors	RP: Determine the role of EGFR in RHAMMB (receptor for hyaluronan-mediated motility isoform B) induced liver metastasis; determine the clinical relevance of RHAMMB in human pancreatic neuroendocrine tumors. MR: Military missions benefit when the military families are healthy and well.
CA093469 Pediatric Brain Tumor only	Gilbertson: Guy: Ellison: Malkin	$1,786,229	St. Jude Children's Research Hospital: Hospital for Sick Children	Molecular-Targeted Therapies of Childhood Choroid Plexus Carcinoma	RP: Large throughput screening to study candidate oncogenes and potential drug targets for rare cancers.. The study validated the overlapping human and mouse genetics and initiated the first whole genome sequencing of CPC. The study screened 1.26 million compounds in the primary round and 688 compounds in the secondary round and identified 23 hits. The highest hit was gemcitabine, an FDA approved drug. The study selected 5 compounds for preclinical study. MR: Development of cost-efficient screening techniques for rare diseases will benefit military medicine.
CA100157 Pediatric Brain Tumors	Read	$465,000	Emory University	Identification and Characterization of Metastatic Cancer Stem Cells in Medulloblastoma	RP: The purpose of this study is to identify and characterize the cells responsible for metastatic disease in medulloblastoma patients, identify genetic markers that predict metastasis, and find novel molecular target for therapeutics. The study found that smo/smo and ptc +/- primary medulloblastoma could be propagated by CD15+/Math1+ cancer stem cells. The study also identified a unique protein, Math1, which allowed the separation of live metastatic cancer cells from spinal cord. MR: Epidemiology studies have shown that several forms of cancer including pediatric brain tumors have higher incidence in military populations compared to the general population. Environmental exposure to cytotoxic and chemical carcinogens could be a contributing factor.
CA100335 Pediatric Brain Tumors	Keating	$450,843	University of Colorado Denver	Targeting Pediatric Glioma with Apoptosis and Autophagy Manipulation	RP: Study seeks to understand the molecular signaling mechanisms involved in pediatric glioma cell survival with the goal to manipulate them and develop novel efficacious therapies. The study confirmed the upregulation of autophagy by MerTK and Axl shRNA inhibition in several human glioma cell lines. MR: The health and welfare of the force is partially determined by the health and welfare of their supportive family. Military missions benefit when the warfighters' families are healthy and well.

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CA100469 Pediatric Brain Tumors	Zong	$531,373	University of Oregon	Social Behavior in Medulloblastoma: Functional Analysis of Tumor-Supporting Glial Cells	RP: Investigation into the fundamentals of understanding the crosstalk between glial cells and medulloblastomaThe study found that glial-ablation treatment resulted in complete remission of tumor. Such treatment was also effective for late-stage tumors. MR: The health and welfare of the force is partially determined by the health and welfare of their supportive family. Military missions benefit when the warfighters' families are healthy and well.
CA100601 Pediatric Brain Tumors	Becher	$456,583	Duke University	Genetically Engineered Mouse Model of Diffuse Intrinsic Pontine Glioma as a Preclinical Tool	RP: Development of valid animal models to promote understanding of tumorigenesis, safety, and toxicities of therapies and identification of novel therapeutic targets and/or resistance mechanisms. The study generated several glioma (DIPG) mouse models: p53 deficient DIPG, PTEN deficient DIPG, p53 and PTEN deficient DIPG. MR: The health and welfare of the force is determined by the health and welfare of their supportive family. Military missions benefit when the warfighters' families are healthy and well.
CA100735 Pediatric Brain Tumors	Paddison	$511,136	Fred Hutchinson Cancer Research Center	Pediatric Glioblastoma Therapies Based on Patient-Derived Stem Cell Resources	RP: Isolation and characterization of glioma stem cells (GSC) from pediatric patients in orthotopic xenograft mouse models and the assessment of whether they diverge from adult GSC. The PI isolated pediatric glioma stem cells (GCS) and developed a protocol for Glioblastoma multiforme (GBM) tumor classification from RNA-sequencing data. MR: The health and welfare of the force is partially determined by the health and welfare of their supportive family. Military missions benefit when the warfighters' families are healthy and well.
CA101163 Pediatric Brain Tumors	Li	$117,975	Baylor College of Medicine	Harnessing Autopsied DIPG Tumor Tissues for Orthotopic Xenograft Model Development in the Brain Stems of SCID Mice	RP: Development of mouse model to better understand carcinogenesis and its treatment. Two orthotopic xenograft models for DPIG were created via the engrafting of autopsy tumor cells into the brains of SCID mice and it was demonstrated that xenograft tumors could replicate key histopathological features of the original tumor. One manuscript in preparation. MR: Advancing genetic research has a direct application to active, reserve and retired U.S. military personnel and their families, as a military lifestyle entails potential exposure to carcinogens known and presumed, chemical and physical/radioactive in nature, both in training and in deployment, and related to equipment utilization and/or combat.

Log Number/ Topic Area	Principal Investigator	Amount	Institution	Application Title	Research Project (RP) and Military Relevance (MR)
CA120021 Pediatric Brain Tumors	Veiseh	Under Negotiation	Massachusetts Institute of Technology	Combinatorial Synthesis and Screening of Nanoparticle Libraries for Delivery of siRNA to Pediatric Brain Tumors across the Blood-Brain Barrier	RP: synthesize and screen nanoparticle libraries for delivery of siRNA across the blood brain barrier designed to interfere with expression of the oncogene N-myc for treatment of medulloblastoma. MR: A healthy family unit, free of serious illnesses, allows the service member to focus on their assigned duty and facilitates the overall military mission.
CA120318 Pediatric Brain Tumors	Huang	Under Negotiation	Cornell University, Weill Medical College	Characterizing and Targeting Bone Marrow-Derived Inflammatory Cells in Driving the Malignancy and Progression of Childhood Astrocytic Brain Tumors	RP: Study the functions of bone marrow derived inflammatory cells (BMDC) in the progression of pediatric glioma and develop therapeutic strategies to target a specific population of BMDCs to suppress the malignant transformation of gliomas. MR: Military missions benefit when the military families are healthy and well.
CA110045 Pediatric cancer	Garcia	$334,476	North Carolina, University of, Chapel Hill	Aspm, a Key Element in Medulloblastoma Pathogenesis and a Novel Target for Treatment	RP: To test the hypothesis that Aspm, a growth-promoting gene required for cerebellar development, is subsequently drafted into the process of medulloblastoma formation. Research has just been initiated. MR: The health and welfare of the force is partially determined by the health and welfare of their supportive family. Military missions benefit when the warfighters' families are healthy and well.
CA110089 Pediatric cancer	Shi	$381,600	Texas, University of, Southwestern Medical Center at Dallas	Function of Brg1 Chromatin Remodeling Factor in Sonic Hedgehog-Dependent Medulloblastoma Initiation and Maintenance	RP: To determine the function of Brg1 in Shh signaling-activated medulloblastoma tumor formation and progression. Research has just been initiated. MR: The health and welfare of the force is partially determined by the health and welfare of their supportive family. Military missions benefit when the warfighters' families are healthy and well.

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CA110407 Pediatric cancer	Jedlicka	$308,584	Colorado, University of, Denver, Anschutz Medical Campus	Hypoxia in Ewing Sarcoma Stem Cell Properties and Drug Resistance	RP: To evaluate the inhibition of hypoxia inducible factor complex using microRNAs to see if they will inhibit the stem cell-like properties of Ewing Sarcoma cells, thus increasing their sensitivity to chemotherapy. Research has just been initiated. MR: The health and welfare of the force is partially determined by the health and welfare of their supportive family. Military missions benefit when the warfighters' families are healthy and well.