REPORT TO THE U.S. CONGRESS

U.S. ARMY MEDICAL RESEARCH AND MATERIEL COMMAND

CONGRESSIONALLY DIRECTED MEDICAL RESEARCH PROGRAMS

PEER REVIEWED CANCER RESEARCH PROGRAM

21 February 2012

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Peer Reviewed Cancer Research Program
Report to Congress

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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). Congressional appropriations totaling over $6 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 breast, prostate, lung, ovarian, melanoma and genetic cancers; pediatric brain tumors, neurofibromatosis; tuberous sclerosis complex; autism; Gulf War illness; psychological health and traumatic brain injury; deployment-related medical; and other research. 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 applications, preproposal screening and invitation to submit full applications, full applications receipt and review, recommendation of grants for funding, and oversight of research grants.

Following receipt of appropriations, each program's Integration Panel, an external advisory board of leading scientists, clinicians, military members, and 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. Integration Panel members are not allowed to be involved either as collaborators or participants in the application processes including, but not limited to, concept design, application development, and conduct of research.

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 a unique application review model based upon recommendations from the Institute of Medicine (IOM) 1993 report.[1] The IOM recommended a two-tier 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, 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 Integration Panel. 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 Commanding General (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 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]

Funds were appropriated through Public Law 111-8 for the Peer-Reviewed Cancer Research Program (PRCRP) in Fiscal Year in 2009 at the amount of $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. Continuing in Fiscal Years 2010 and 2011 funds were appropriated through Public Laws 111-118 and 112-10 respectively for the PRCRP. Various committee reports or joint explanatory statements contained funding tables and Congressional language regarding these programs. For FY12 funds were appropriated through Public Law 112-74. The Military Construction and Veterans Affairs and Related Agencies Appropriations Act, 2012, Conference Report 112-331 requires a detailed status of the PRCRP for which an appropriation of $12.8M was directed, including research progress, accomplishments, and relevance to service members and their families. This report provides a 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-FY11 PEER REVIEWED CANCER RESEARCH PROGRAM

Funds were appropriated through Public Law 111-8 for the PRCRP in FY09 at the amount of $16M. 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, $15M of funds were appropriated through Public Law 111-118 for the PRCRP to fund cancer research 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.

In April 2011, funds were appropriated in the amount of $16M for the PRCRP by the Public Law 112-10. 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 is planned for January 2012, and programmatic review is planned for March 2012. The final recommendation for funding list will be sent to the CG, USAMRMC for approval and grant negotiations will ensue. Final award agreements for the FY11 PRCRP are expected no later than 30 September 2012.

FY12 PEER REVIEWED CANCER RESEARCH PROGRAM

For the current fiscal year (FY12), Military Construction and Veterans Affairs and Related Agencies Appropriations Act, 2012, Conference Report 112-331 requires a detailed status of the PRCRP for which $12.8M was appropriated through Public Law 112-74, including research progress, accomplishments, and relevance to service members and their families. 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. 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 will be held in March 2012 with program announcements released in May and June 2012. Pre-application receipt will be in late July 2012. Pre-application screening will be planned for August/September 2012. Application receipt will be scheduled for

November 2012 with peer review in January 2013. Programmatic review will be scheduled for March 2013, and award obligation will be no later than 30 September 2013.

RESEARCH AREA INVESTMENT AND PROGRESS

For FY09 and FY10, 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. Additionally, mesothelioma, pancreatic cancer, pediatric cancers (other than pediatric brain tumor research), and radiation protection utilizing nanotechnology are not included because review processes for the FY11 cycle have not been finalized.

A tabular summary of the proposed work and progress for each of the obligated awards for FY09 and FY10 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 FY09 and FY10 award. FY11 and FY12 funds will be awarded no later than 30 September 2012 and 30 September 2013, respectively. Research will be initiated 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 due to the nature of their service and deployments 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]

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[7,8] incidence of melanoma, testicular, thyroid, cervical, and vulvar cancers in the Air Force population,[7] particularly cervical and vulvar cancer. Another review demonstrated a higher rate of prostate cancer in the military beneficiary population compared to the general population.[9]

Hodgkin's disease, a blood cancer, was the most common cancer diagnosis in men.[10] 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.[11] 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.[12] 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.[13] As the configuration of the military population changes to include more women, consideration into research on their risks and exposures is critical.

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.[14] 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.[12] As shown by Hicks et al,[15] 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.[16] The cost of cancer care within the Military Health System in FY02 was over $1 billion.[16] 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-FY12 PRCRP using its established and highly recognized management process. By funding research into cancers that potentially result with higher incidence due to exposures in military environments, the FY12 PRCRP may provide beneficial future medical data and information that may contribute to developing medical treatments or procedures to improve the health outcomes of military members and their families. The CDMRP will plan, execute, and manage the FY09-FY12 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

Fiscal Year (FY) Topic Area Included[1]	Topic Area	Total Invested Dollars ($) FY09-FY10
2010	Blood Cancer	2,059,253
2010	Colorectal Cancer	1,982,333
2009-2010	Genetic Cancer[2]	10,073,383
2010	Kidney Cancer	1,776,990
2010	*Listeria* Vaccine for Cancer	543,000
2009-2010	Melanoma and Other Skin Cancers[3]	5,076,740
2009	Non-invasive Cancer Ablation Therapy[4]	1,753,431
2009-2010	Pediatric Brain Tumor	4,319,139
2010	Radiation Protection utilizing nanotechnology[5]	0
	Total Investment in Research Dollars[6]	$27,584,269

[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-FY10 was $31 million; total investment in research dollars is less USAMRMC and CDMRP management costs (~8.8%).

APPENDIX B: FISCAL YEAR 2009 (FY09)-FY10 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). 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).
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 developed. Research has just been initiated. 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. 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.

*No applications from the FY10 topic area radiation protection utilizing nanotechnology were selected for funding.

Log Number/ Topic Area	Principal Investigator	Amount	Institution	Application Title	Research Project (RP) and Military Relevance (MR)
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 (CRC). 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 models. 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.
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. MR: The understanding of critical pathways to resistance will support military cancer treatment of service members and their families.
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. 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.

Log Number/ Topic Area	Principal Investigator	Amount	Institution	Application Title	Research Project (RP) and Military Relevance (MR)
CA093139 Genetic Cancer	Cao	$559,548	Clemson University	New Protein Modification under Nitrosative Stress	RP: Reactive nitrogen species leads to unstable DNA and carcinogenesis. Outcomes: Two publications: (1) Lee H, Brice A, Wright C, et al. 2011. *J Biol Chem* 285:41483-41490. (2) Mi R, Abole AK, and Cao W. 2011. *Nucleic Acids Res* 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. 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. 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. MR: Deployment to areas of high ultraviolet (UV) exposures puts service members at increased risk for the development of melanoma and other skin cancers.

Log Number/ Topic Area	Principal Investigator	Amount	Institution	Application Title	Research Project (RP) and Military Relevance (MR)
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. 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. 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. 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. Outcomes: Four meeting abstracts. MR: Radiation exposure is of high risk in military populations.

Log Number/ Topic Area	Principal Investigator	Amount	Institution	Application Title	Research Project (RP) and Military Relevance (MR)
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. 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. Outcome: One meeting presentation. 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. Outcome: One meeting abstract. MR: Deployment to areas of high UV exposures puts service members at increased risk for the development of melanoma and other skin cancers.

Log Number/ Topic Area	Principal Investigator	Amount	Institution	Application Title	Research Project (RP) and Military Relevance (MR)
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. 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. 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. 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. Outcome: One publication: Challagundla KB et al. 2011. *Mol Cell Biol* 31:4007. MR: Exposure to environmental hazards/stress in military personnel is associated with increased cancer risks. Biomedical studies of hazardous environmental exposures that may causes damage to DNA and long-term health care issues such as cancer will be beneficial to military personnel.

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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 from mouse models of t-AML/t-MDS induced by alkylating agents or ionizing radiation. 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. 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 tumors. 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. 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	Case Western Reserve University	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. 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. 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.
CA100587 Kidney Cancer Research	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. 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 Research	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. 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 Research	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. 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.
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 for enhanced immunoresponse for cancer vaccination. MR: The development of immune enhanced technology will benefit military medicine from cancer to infectious diseases (a main exposure risk in deployed military populations).
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. Research has just been initiated. 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.
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. Research has just been initiated. 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.

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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. 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 an effective tumor immunity. 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.
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.
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. 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.

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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. Ongoing study. Outcomes: Two published manuscripts: (1) Gaziel-Sovran A, Segura MF, Di Micco R, et al. 2011. *Cancer Cell* 20(1):104-118. (2) Zakrzewski J, Geraghty LN, Rose AE, et al. 2011. *Cancer* 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. 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.
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). 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.
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. MR: Development of a new treatment modality for tumor ablation may translate to expansive medical methodologies with military benefit.

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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. Outcomes: Meeting presentations and invention disclosure submitted to the Technology Transfer office at Case Western Reserve University. 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	Wake Forest University Health Sciences	Targeted Nanoparticles for Kidney Cancer Therapy	RP: Development of novel optically activated multifunctional nanotubes to target and kill renal 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.
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: Multiple meeting presentations. 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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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. 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. Research has just been initiated. 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. 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.
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 medulloblastoma. 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. 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.

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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. 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. 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.