FISCAL YEAR 2016
REPORT TO CONGRESS

U.S. ARMY MEDICAL RESEARCH AND MATERIEL COMMAND

CONGRESSIONALLY DIRECTED MEDICAL RESEARCH PROGRAMS

PEER REVIEWED CANCER RESEARCH PROGRAM

September 2017

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Peer Reviewed Cancer Research Program
Fiscal Year 2016 Report to Congress

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BACKGROUND

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 Army biomedical research and development programs and selected programs within the Department of Defense (DoD) Defense Health Program (DHP). As directed by the Office of the Assistant Secretary of Defense for Health Affairs (OASD(HA)), the Defense Health Agency (DHA) J9, Research and Development Directorate manages the DHP Research, Development, Test, and Evaluation (RDT&E) appropriations, including funds for the Peer Reviewed Cancer Research Program (PRCRP). The USAMRMC Congressionally Directed Medical Research Programs (CDMRP) manages the PRCRP in support of the OASD(HA) and the DHA.

PURPOSE OF REPORT

This report is in response to the Senate Report 114-63, page 201, and House Report 114-139, page 278 that accompanied H.R. 2675, the Department of Defense Appropriations Bill for Fiscal Year (FY) 2016 directing the ASD(HA) to submit a report to the Congressional defense committees on the status of the PRCRP. For each research area, the report should include the funding amount awarded, the progress of research, and the relevance to Service members and their families. This report provides an update on the detailed status of the FY09-FY16 PRCRP, research accomplishments, and the relevance of PRCRP-supported research to Service members and their families.

FY09-FY16 PEER REVIEWED CANCER RESEARCH PROGRAM STATISTICS

From its inception in FY09 through the current fiscal year, Congressional language has directed the amount to be appropriated for the PRCRP as well as the different topic areas to be funded (Table 1). The majority of funds directed to the PRCRP are invested in research (Figure 1) while management and withhold costs are kept low. In FY16, 92% of the PRCRP appropriation went toward research and 8% toward management costs.

For each research topic area designated by Congress, the PRCRP has solicited and reviewed pre-applications, and received, reviewed, and awarded full applications. From FY09 through FY16, the PRCRP had a funding rate of nearly 14% across a broad range of topic areas. In FY16, the PRCRP funded 72 applications (representing 90 separate awards) of the 400 full applications received for an 18% funding rate. FY16 awards are expected to initiate research by 1 October 2017. Outcomes are expected by the end of the periods of performance, which is within 2 to 4 years of the start date of each award.

TABLE 1: PRCRP Appropriation and Topic Areas per Fiscal Year

Fiscal Year	Public Law	Appropriation	Topic Areas*	Awards‡
2009	110-329	$16 million (M)	$4M, Melanoma and other skin cancers as related to deployments of Service members to areas of high exposure; $2M, Pediatric brain tumors within the field of childhood cancer research; $8M, Genetic cancer and its relation to exposure to the various environments that are unique to a military lifestyle; and $2M, Noninvasive cancer ablation treatment including selective targeting with nanoparticles	38
2010	111-118	$15M	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; Radiation protection utilizing nanotechnology	30
2011	112-10	$16M	Melanoma and other skin cancers; Pediatric cancer research; Genetic cancer research; Kidney cancer; Blood cancer; Colorectal cancer; Pancreatic cancer; Mesothelioma; *Listeria* vaccine for cancer; and Radiation protection utilizing nanotechnology	44
2012	112-74	$12.8M	Melanoma and other skin cancers; Pediatric brain tumors; Genetic cancer; Pancreatic cancer; Kidney cancer; Blood cancer; Colorectal cancer; Mesothelioma; and *Listeria* vaccine for cancer	27
2013	113-6	$15M	Melanoma and other skin cancers; Pediatric brain tumors; Genetic cancer; Pancreatic cancer; Kidney cancer; Blood cancer; Colorectal cancer; Mesothelioma; and Neuroblastoma	27
2014	113-76	$25M	Blood cancer; Colorectal cancer; Genetic cancer research; Kidney cancer; *Listeria* vaccine for cancer; Melanoma and other skin cancers; Mesothelioma; Myeloproliferative disorders; Neuroblastoma; Pancreatic cancer; Pediatric brain tumors; and Cancers related to radiation exposure	47
2015	113-235	$50M	Colorectal cancer; Genetic cancer research; Kidney cancer; Listeria vaccine for cancer; Liver cancer; Melanoma and other skin cancers; Mesothelioma; Myeloproliferative disorders; Neuroblastoma; Pancreatic cancer; Stomach cancer	110
2016	114-113	$50M	Bladder cancer; Colorectal cancer; Immunotherapy; Kidney cancer; Listeria vaccine for cancer; Liver cancer; Lymphoma; Melanoma and other skin cancers; Mesothelioma; Myeloproliferative disorders; Neuroblastoma; Pancreatic cancer; Pediatric brain tumor; Stomach cancer	90†

*Topic areas are designated by Congressional language as published in the specified Public Law, Congressional Record, and post-Presidential signature communications for clarification on language.
†FY16 recommended awards were Openotiation at the time of this writing and could change once negotiations are complete.
‡Number of awards represents all open, pending close-out, and closed awards; does not include withdrawals.

Over the years, PRCRP has funded and managed numerous topic areas as directed by Congress. Figure 1 shows the percentage of dollars invested in each topic area from FY09-FY16. In each fiscal year, the investment portfolio is affected by many factors including: whether or not a topic area is present, the application receipt with respect to each topic area, the merit of the science and the impact of the proposed outcomes, and the appropriation amount with respect to the number of topic areas. The topic area of *Melanoma and other skin cancers* has been continuously included under the PRCRP since the inception of the program. Other topic areas like *Bladder cancer*, *Immunotherapy*, and *Lymphoma* were new to the PRCRP in FY16. Additionally, each topic area is considered during the programmatic review to ensure a balanced portfolio with respect to the specific fiscal year topic areas. Total research recommended for funding by topic area for FY16 can be reviewed in Table 2.

FIGURE 1: FY09-FY16 PRCRP Research Investment per Topic Area (% of Total Research Dollars)

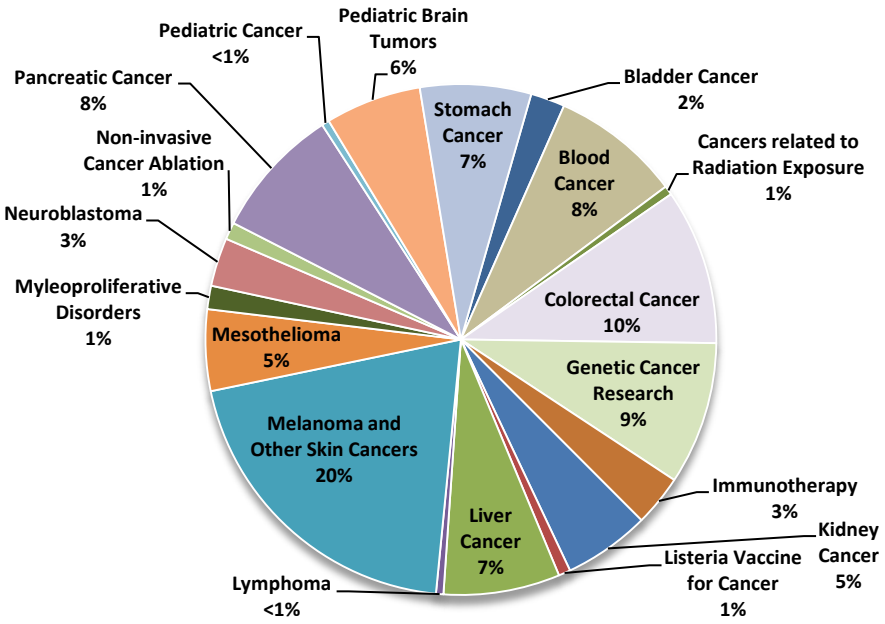

TABLE 2: Total Research Dollars Invested per Topic Area for FY16

Topic Area	Total Dollars Recommended for Investment ($M)
Bladder cancer	5.4
Colorectal cancer	2.3
Immunotherapy	8.4
Kidney cancer	2.7
Listeria vaccine for cancer	0.6
Liver cancer	4.3
Lymphoma	1.2
Melanoma and other skin cancers	5.4
Mesothelioma	2.7
Neuroblastoma	0.6
Pancreatic cancer	3.6
Pediatric brain tumors	4.0
Stomach cancer	6.1
Total Research Investment	**46.8**

CANCER RESEARCH RELEVANCE: SERVICE MEMBERS AND THEIR FAMILIES

The vision of the PRCRP is to improve quality of life by decreasing the impact of cancer on Service members, their families, and the American public. As a funding program, the most significant method the PRCRP has to influence the quality of life of Service members and their families is through creative and impactful funding solicitations that emphasize the health and well-being of the military community.

The FY16 PRCRP sought to support studies that are responsive to at least one of the FY16 Military Relevance Focus Areas (Table 3).

TABLE 3: FY16 Military Relevance Focus Areas

Militarily relevant risk factors associated with cancer (e.g., ionizing radiation, chemicals, infectious agents, and environmental carcinogens)
Gaps in cancer prevention, screening, early detection, diagnosis, treatment, and/or survivorship that may affect the general population but have a particularly profound impact on the health and well-being of military members, Veterans, and their beneficiaries

In the first Military Relevance Focus Area, health risks associated with unique military environments were addressed. Service members, deployed across the world both in developed and developing nations, sustain environmental exposures that have been linked to the development of cancer. Several hazards have been identified that may play a role in the risk of carcinogenesis and the military population. Exposures linked to increased cancer risk include,

but are not limited to, chemical weapons or storage, ionizing radiation, herbicides, electromagnetic fields, jet fuel, organic materials, biological agents, ultraviolet radiation, among others (Table 4).

Detailed analysis by the Automated Central Tumor Registry of DoD-published data demonstrated that the incidence of melanoma was higher in the U.S. military population in comparison to the U.S. general population.[1] Lea et al., reported that the incidence rates of melanoma in active duty military personnel were higher than the population-based registry in the U.S.[2] This study also showed that Air Force personnel had the highest incidence rates of melanoma in the military.

Over the years, the PRCRP has funded innovative research in the *Melanoma and other skin cancers* topic area. The PRCRP has invested more than 20% of total available research funds in melanoma and other skin cancers research (Figure 2). Supported by an Idea Award with Special Focus funded in FY14, Dr. Jin Xie of the University of Georgia is approaching the treatment of malignant melanoma through an innovative methodology called X-ray induced photodynamic therapy for lung metastasis. This technology uses nanosensitizers coupled to a tumor-targeting ligand that home to metastasized tumors in the lung. Study results have shown these nanosensitizers to be effective in killing cancer cells while maintaining low systemic toxicity.

Additionally, it is known that exposures other than ultraviolet light cause many different cancers. Known carcinogens may lead to different cancers in military members. The Department of Veterans Affairs (VA) has acknowledged that certain exposures increase the cancer risk of Service members and their families (Table 4). 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 with subjects who had not served in Vietnam.[3,4] 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.[5] Additionally, the U.S. Congress has tasked the National Academy of Medicine (previously known as the Institute of Medicine) to deliver a report every 2 years on the health effects of Agent Orange exposure. The latest report,[6] titled *Veterans and Agent Orange: Update 2014*, analyzed the herbicide and cancer risk and revealed sufficient evidence of an association between exposure and cancer development for soft tissue sarcomas, non-Hodgkin's lymphoma, Hodgkin's disease, and chronic lymphocytic leukemia. It also provided suggestive evidence of an association between exposure and development of cancers including lung, prostate, bladder, and multiple myeloma.

Service members are deployed to different environments with various health hazards. While utilization of exposed asbestos as a building material in the U.S. has declined, many countries where our Service members are deployed still rely on asbestos as a major material for housing and building manufacturing.[7] In the developing world, exposure to asbestos is a cancer risk, causing cancers such as mesothelioma, lung cancer, cancer of the larynx, pharynx (throat), stomach, colon, and rectum.[8] Asbestos-related diseases such as mesothelioma are a known risk to Naval shipyard work.[9] A new study by the Centers for Disease Control and Prevention (CDC)[10] reported a rise in mesothelioma deaths by 5% from 1999 to 2015. Thus, asbestos and other elongated mineral particles still affect cancer risk. In FY16, the PRCRP invested in studies

to understand asbestos exposures, supporting Dr. David Harpole, from Duke University, and Dr. Raphael Bueno, from Brigham and Women's Hospital, who are working together on an FY16 PRCRP Translation Team Science Award to define the genetic alterations that drive malignant plural mesothelioma (MPM) development. Using large collections of civilian and Veteran tissue samples, they aim to refine the classification of MPM into biologically and prognostically distinct subgroups. MPM is most commonly traced to occupational exposure to asbestos. The team will therefore compare the subgroup clustering between the civilian and military populations to determine which prognostic biomarkers are shared or distinct among the two groups.

TABLE 4: Malignancies Associated with Military Service*

Exposure Related Cancer Concerns for Service Members	
	**Agent Orange** Chronic B-cell leukemia; Hodgkin's disease; multiple myeloma; non-Hodgkin's lymphoma; respiratory cancers; soft tissue sarcomas, bladder cancer
	**Asbestos** Mesothelioma; gastrointestinal, colorectal, throat, kidney, esophagus, and gall bladder cancers
	**Industrial Solvents** Leukemia; liver cancer; bilary tract cancer; kidney cancer; non-Hodgkin's lymphoma; brain cancer; blood cancer
	**Infectious Agents** Anogenital cancers; cervical cancer; Burkitt lymphoma; hepatocellular carcinoma; Kaposi sarcoma; leukemia, gastric cancers, head and neck cancer
	**Radiation** All cancers, but in particular, cancers of the bile ducts, bone, brain, breast, colon, esophagus, gall bladder, liver, lung, pancreas, pharynx, ovary, salivary gland, small intestine, stomach, thyroid, and urinary tract; leukemia (except chronic lymphocytic leukemia); lymphomas (except Hodgkin's); multiple myeloma
	**Ultraviolet Light** Melanoma; basal cell carcinoma; squamous cell carcinoma; other skin cancers

*Sources: U.S. Department of Veteran's Affairs, Public Health; http://www.publichealth.va.gov/exposures/index.asp; http://www.infectagentscancer.com; http://www.va.gov/vetapp07/files2/0717857.txt

Another high-risk hazard for military members is potential exposure to ionizing radiation. Congress has tasked the PRCRP to answer unmet biomedical research needs of our military on

several occasions including events such as the Fukushima disaster in Japan and the resulting potential radiation contamination. In FY14, Congress added the topic area *cancers related to radiation exposure* to the PRCRP. This resulted in funding in this topic area of nearly $1M for two FY14 PRCRP Idea Awards with Special Focus. In his FY14 PRCRP award, Dr. Mohan Natarajan from the University of Texas Health Science Center at San Antonio is studying how radiation exposure alters free radical signaling, a component of oxidative stress, in a model of blood vessels, which are the tissues most susceptible to radiation. Dr. Natarajan used the in vitro blood vessel model to demonstrate that the shear stress experienced by blood vessels combined with exposure to radiation resulted in increased oxidative stress as compared with controls that experienced neither shear stress nor radiation. He also developed mouse models that will be used during the second year of the award for in vivo studies on the acute and delayed effects of radiation-induced development of cancer. In the second award under the topic area *cancers related to radiation exposure,* Dr. Nelson Chao from Duke University looked at how radiation exposure can transform hematopoietic cells. These transformed cells evade the immune system and may become malignant. Dr. Chao made progress linking a specific kinase to the initiation and progression of lymphoma and myeloma. He also made further strides assessing a small-molecule therapeutic that, when administered after radiation exposure, may mitigate cancer development. Based on these results, Dr. Chao obtained a provisional patent.

In addition to ionizing radiation and chemical exposures that may lead to cancer, Service members, their families, and Veterans are also susceptible to infectious agents that increase the risk of cancer development. It is estimated that over 18% of cancers, such as gastric adenocarcinoma, cervical carcinoma, and hepatocarcinoma, may be a result of infections.[11] Service members are increasingly presenting with sero-positive scores for infectious agents such as *Helicobacter pylori.*[12] These Service members may be more at risk for chronic inflammation and the development of cancers of the gastrointestinal tract. The majority of patients diagnosed with gastric cancer present with incurable, late-stage disease because early-stage gastric cancer is often asymptomatic, and there are currently no established screening tests. Gastric cancer incidence has recently been on the rise in individuals aged 25 to 39, the age of the majority of the active duty force. With an FY15 PRCRP Career Development Award, Dr. Ying Bao of Brigham and Women's Hospital is using plasma samples to measure systemic metabolic changes associated with gastric cancer growth to identify the first-ever metabolomic fingerprint that could be used to detect gastric cancer at its earliest stages, when a cure is still attainable. Moreover, identification of gastric cancer-associated metabolites and their pathways could provide new targets for preventative and therapeutic interventions.

Other infectious agents are hazardous exposure agents as well for Service members, their families, and other military beneficiaries. Kaposi sarcoma-associated herpesvirus (KSHV) can cause several types of cancers in immune-compromised individuals, including primary effusion lymphoma (PEL). PEL is a rapidly progressing type of lymphoma that is commonly diagnosed in HIV/AIDS patients. In FY14, Dr. Zhiqiang Qin, from Louisiana State University's Health Sciences Center, received a PRCRP Career Development Award under the *blood cancer* topic area to investigate the role of hepatocyte growth factor (HGF) and its receptor (c-Met) in PEL pathogenesis. Using an immune-deficient xenograft mouse model, Dr. Qin is testing whether a selective small-molecule inhibitor of c-MET, PF-2341066, can slow PEL progression and reduce established tumors. PF-2341066 reduced HGF production and effectively prevented PEL

expansion in a xenograft model. Notably, eight peer-reviewed publications have resulted from this research, including outcomes published in *Blood*, demonstrating that targeting the HGF/c-MET pathway induced KSHV and PEL cell apoptosis through cell cycle arrest and DNA damage to the cancer cells.[13] Dr. Qin hopes to use these results to support future clinical trials that will evaluate strategies to target HGF/c-MET for the treatment of deadly, virus-associated lymphomas.

Exposures are not the only cancer risk factors to Service members, their families, and other beneficiaries. Table 3 also delineates the second PRCRP Military Relevance Focus Area for investigators to study: the cancer care spectrum. The cancer care spectrum covers research from prevention to detection/diagnosis, to prognosis, to treatment, and, finally, to survivorship. Along this research and care spectrum, knowledge gaps may affect the general population but have a particularly profound impact on the health and well-being of Service members and *mission readiness*. A cancer diagnosis of a Service member affects not only the individual Soldier, Airman, Marine, or Sailor; it will affect every part of the unit and mission. Each individual plays a critical role in mission readiness. To have a Service member at risk or under treatment decreases the mission readiness of the unit. This extends to Service members' families. When a member of a Service member's family receives a diagnosis of cancer, the Service member is affected as well. Such a crisis striking the Service member's primary support system may lead to a request for transfer, exceptional status, or even separation. All of these actions lead to the reaction of a mission readiness effect. Therefore, the second military relevance focus area of the PRCRP strives to answer this call by targeting knowledge gaps and funding areas of research in dire need so that Service members can be ready when called to duty.

In prevention, the PRCRP funded an FY15 Idea Award with Special Focus to support Dr. Yujin Hosida, from the Icahn School of Medicine at Mount Sinai, in developing a cell culture model that uses oncogenic variants of the hepatitis C virus for fast-track identification of cancer prevention targets and biomarkers in liver cancer. This would identify molecular changes made after viral clearance and thus show the lasting effects of infection and possible cancer risk. This is an important step forward in studying the relationship between viral infection and cancer development in the military.

A critical need in patient care is diagnosis and detection of cancers early enough that treatment may be effective. Dr. Brian Wolpin of the Dana-Farber Cancer Institute, supported by an FY13 PRCRP Career Development Award, is seeking to understand pancreatic cancers, one of the most difficult cancers to detect and treat. Most pancreatic cancers are discovered at late stages and treatment options are minimal with most succumbing to their disease within a year of diagnosis. Dr. Wolpin is studying how pancreatic cancers use nutrients to promote their growth, his hypothesis being that unique metabolic changes may signal early pancreatic cancer. Currently, over 2,000 plasma metabolites of pancreatic cancers and controls have been identified and are under investigation to be analyzed for a signature of pancreatic cancer.

Bladder cancer is among the 10 most common cancers diagnosed. One of the most prominent bladder cancers, non-muscle invasive bladder cancer (NMIBC), can be detected and treated early; however, treatments are limited, and patients experience side effects and are still at high risk of recurrence (http://www.bcan.org/). Dr. Youngjae You and his team at the University of

Oklahoma were awarded an FY16 PRCRP Idea Award with Special Focus to support the development of a novel prodrug system to target and deliver chemotherapy to cancer cells. The idea is to use the Food and Drug Administration (FDA)-approved technology of the formation of a photosensitizer (protoporphyrin IX) within a cancer cell to target light-activatable prodrugs to those cancer cells. Photodynamic therapy using visible light will then activate the prodrug to its cytotoxic form, ultimately resulting in the ablation of the cancer cells with minimal systemic side effects. If successful, this site-specific chemotherapy technology could improve therapeutic efficacy, alleviate side effects, and reduce the recurrence rate of NMIBC. Moreover, this technology can be applied to various types of cancers.

The PRCRP continues to fund meritorious research for the benefit of Service members and their families and to improve the quality of life for those impacted by a cancer diagnosis. A healthy family unit, free of serious illnesses, allows the Service member to focus on his or her role as a Warfighter and facilitates the overarching military mission. There are over 300,000 military beneficiaries with a cancer diagnosis, for a prevalence of 4.1%, comprised of more than 60 different cancer types.[14] The cost of cancer care within the Military Health System (MHS) in FY02 was over $1 billion.[14] As shown by Lee et al., the MHS continues to diagnose and treat active duty Service members for a wide variety of cancers.[15] Funding studies on the detection, diagnosis, treatment, and prevention of these diseases benefits both the Warfighters and the American public, ultimately leading to increased survival rates and decreased costs of medical care.

SUMMARY OF RELEVANCE AND PROGRESS OF PRCRP AWARDS

Table 5 includes a summary of all open and pending awards as of 31 July 2016. In accordance with the Congressional language: '*For each research area, the report should include the funding amount awarded, the progress of the research, and the relevance of the research to Servicemembers*'. To represent a complete report, the FY17 PRCRP Report to Congress includes the log number, topic area, last name of Principal Investigator (PI), award amount, institution, title, research progress, and military relevance are noted for each award funded from FY09-FY16. For information on closed awards (awards where the period of performance has expired), see Appendix A.

TABLE 5: Research Progress and Military Relevance of Open, and Period of Performance Expiring (POP Exp) Awards

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Bladder Cancer				
CA160108 $558,000 Open	Williams/ The University of Texas Medical Branch at Galveston	Agent Orange Exposure and Bladder Cancer	RP: The PI will data mine the VA Health System to determine whether Agent Orange (AO) exposure is linked with bladder cancer (BC) risk and bladder cancer-specific mortality. MR: If the aims of this proposal prove true, this information will be made available to all Service members, Veterans, and their families who may be at increased risk for BC. Long-term outcomes may be improved by screening measures to identify patients sooner, when the disease is the most curable.	*Research initiated*
CA160212 $610,199 Open	Faltas/ Cornell University, Weill Medical College	Dissecting the Role of APOBEC3 Mutagenic Proteins as Drivers of Genomic Instability and Chemotherapy Resistance in Urothelial Carcinoma	RP: The PI will test the hypothesis that APOBEC3 proteins drive the development of chemotherapy-resistant urothelial carcinoma (UC) by mutating single-stranded DNA, inducing genomic instability and mutations that fuel the evolution of chemotherapy-resistant clones. MR: Within the VA population, UC is the fourth most common cancer. UC is also associated with several risk factors that are relatively common in the Veteran and active duty Service member populations such as smoking and exposure to agent blue and industrial solvents (Institute of Medicine, 2014).	*Research initiated*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Bladder Cancer				
CA160300 $673,356 Open	Galsky/ Icahn School of Medicine at Mount Sinai	Circulating Tumor Cell-Based Patient-Derived Xenograft Models of Metastatic Bladder Cancer as a Platform for Development of Novel Therapeutic Approaches	RP: The PI hypothesizes that patient-derived xenograft models generated from circulating bladder cancer cells (CTC-PDX models) can be used to identify targetable mechanisms of cisplatin resistance. The proposal aims to expand and molecularly profile this innovative model system platform, characterize the DNA damage response mechanisms that contribute to cisplatin resistance, and identify novel therapeutic approaches. MR: Bladder cancer represents the fourth most common type of cancer diagnosed in VA Health System; tobacco use is the major risk factor. Recent studies indicate that active duty military personnel and Veterans are more likely to smoke than the general US adult population and that military personnel who have been deployed are more likely to smoke than those who have not been deployed. Addressing sources of tobacco-related morbidity and mortality has clear and important implications for military Service members, Veterans, and their beneficiaries.	*Research initiated*
CA160312/P1/P2 $1,546,081 Open	Rosenberg/ Memorial Sloan Kettering Cancer Center McConkey/ Johns Hopkins University Van Allen/ Dana-Farber Cancer Institute	Precision Medicine in Platinum-Treated Lethal Bladder Cancer	RP: The three partnering PIs on this award will use pretreatment samples collected as part of a Phase III trial of gemcitabine and cisplatin plus bevacizumab treatment or placebo to determine: the association between DNA damage response and repair genes and clinical outcomes of the patients on this trial; the impact of tumor subtypes on response to therapy; and the underlying mechanism(s) that drive exceptional responses to treatment. The proposed correlative studies will be the largest genomic and transcriptomic analysis of metastatic bladder cancer conducted to date. MR: Military service remains one of the occupations associated with increased risk of bladder cancer, in part due to Agent Orange exposure, and higher rates of bladder cancer-related mortality.	*Research initiated*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Bladder Cancer				
CA160487 $592,000 Open	You/ University of Oklahoma Health Sciences Center	Visible Light-Controlled Combination Strategy for Treating Nonmuscle Invasive Bladder Cancers	RP: The PI will test the hypothesis that mitochondria-localizing and singlet oxygen -activated prodrug can be effectively activated by cancer cell-specific and mitochondria-specific PpIX (a photosensitizer formed in mitochondria) photodynamic therapy, and thus greatly improves therapeutic efficacy with minimal collateral damage in the bladder. MR: Bladder cancer is the fourth most common cancer in Veterans due to several exposure risks: higher prevalence of smoking than in civilian population, exposure to Agent Orange in Vietnam, and increased exposure to industrial solvents like benzene.	*Research initiated*
CA160685 $549,000 Open	Arora/ Washington University	Determinants of T-Cell Activity in Bladder Cancer	RP: The goal is to better understand the factors that influence bladder cancer immune surveillance and sensitivity to check-point blockade to extend the benefits of immune therapy to a greater number of bladder cancer patients and to maximize the response to therapy. MR: Bladder cancer prevalence in Veterans is two times higher than in the general population. Through the studies proposed here, the PI will develop a better understanding of the barriers to immune rejection of bladder cancer, insights that will ultimately inform new strategies to treat members of the military, Veterans, and their families.	*Research initiated*
CA160715 $624,398 Open	Inman/ Duke University	Synergistic Immuno-Photo-Nanotherapy for Bladder Cancer	RP: The overall objective of this proposal is to optimize SIMPHONY (synergistic immuno-photo-nanotherapy) and demonstrate that it can lead to the generation of highly effective antitumor immunity useful for treating bladder cancer (BC). MR: Tobacco smoking is the most common etiology for BC, and Veterans have a higher incidence of smoking and developing smoking-related cancers. The second most common risk factor in BC etiology is exposure to environmental carcinogens and military personnel are at much higher risk for exposure to bladder cancer-associated carcinogens.	*Research initiated*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Bladder Cancer				
CA160934 $257,100 Open	Wardlaw/ Memorial Sloan Kettering Cancer Center	S-Phase Dynamics of the Mre11 Complex as a Barrier to Cancer	RP: The PI will study the S-phase specific roles of the Mre11 complex (which is typically associated with the DNA damage response), how mutations observed in bladder cancer influence these roles, and determine if this information can be exploited to develop therapeutic targets to treat bladder cancer. MR: As there is a higher prevalence of bladder cancer in Veterans than the civilian population, any advance in understanding the mechanisms in the disease that leads to improved therapeutic options will improve the lives of those affected by bladder cancer.	*Research initiated*
Blood Cancer				
CA120381 $383,998 Open	Reshef/ University of Pennsylvania	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 in treatment of blood cancers.	*Presentations: 2* *Funding obtained: 3 grants*
CA130247 $534,407 Open	Wang/ University of North Carolina at Chapel Hill	Epigenetic Therapy of Hematopoietic Malignancies: Novel Approaches for Tissue-Specific and Global Inhibition of EZH2 Enzymatic Activities	RP: To develop novel means to target two novel proteins of B-cell derived tumors for anticancer therapies and to investigate the mechanism by which these proteins induce B-cell related tumors. MR: Blood cancers, including lymphoma and multiple myeloma, are associated with exposure to chemical and biological agents from the Vietnam and Gulf Wars.	*Publications: 3*
CA130256 $364,538 Open	Lapalombella/ Ohio State University	Understanding and Targeting the Nuclear Export Protein XPO1 in B-Cell Malignancies	RP: To determine the effects of the XPO1 mutations on the development and pathogenesis of chronic lymphocytic leukemia (CLL). MR: CLL is more prevalent in Veterans, particularly in those who served during the Vietnam War, due to the exposure to Agent Orange and other toxins.	*Publication: 1* *Degree/Employment: Obtained a faculty position* *Funding obtained: 3 grants*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Blood Cancer				
CA130371 $270,365 Open	Cardelli/ Louisiana State University Health Sciences Center	Exploring Potential Link between Bacterial Flora, Myeloid-Derived Suppressor Cells (MDSC), and Extraintestinal Tumor Development	RP: To test if germ-free mice will show reduced tumor growth and enhanced antitumor immune response. MR: Military members and their families are exposed to a variety of environmental pollutants, increasing their risk of certain cancers. Frequent changes in geographical locations, accompanying changes in diet, and exposure to environmental pollutants can alter microbiome in military personnel more profoundly than that of the general public who are not subjected to such risk factors.	*None to date*
CA140119 $556,200 Open	Ji/ Northwestern University	The Role of mDia1 in the Aberrant Innate Immune Signaling in del(5q) Myelodysplastic Syndromes	RP: Deletion of chromosome 5 long arm (del(5q)) is the most common genetic defect in patients with myelodysplastic syndromes (MDS). This study is to test the hypothesis that mDia1 deficiency induces aberrant innate immune signaling, critical for the pathogenesis of del(5q) MDS. MR: Pathogen-associated molecular patterns or damage-associated molecular patterns resulting from military deployment could trigger abnormal immune responses that lead to MDS.	*New research – no outcomes reported to date*
CA140236 $610,200 Open	Fontan/ Cornell University Weill Medical College	Nuclear Functions of BCL10 and MALT1 and Their Potential for Therapeutic Intervention in Non-Hodgkins Lymphoma	RP: B-cell lymphoma/leukemia 10 (BCL10) is a key mediator of the immune response. This study is to determine the function of nuclear BCL10 and its role in lymphomagenesis. MR: Military personnel are at greater risk for developing non-Hodgkin's lymphoma (NHL) due to exposure to cytotoxins and chemicals during deployment. Improvement in NHL prognosis and treatment options will benefit the military population.	*New research – no outcomes reported to date*
CA140257 $545,497 Open	Bilgicer/ University of Notre Dame	Rational Engineering of Designer Nanoparticles to Target Multiple Myeloma	RP: To design and evaluate nanoparticles to target multiple myeloma (MM). MR: Chemical exposure such as Agent Orange increase the incidence rate of MM. This project could improve the therapeutic efficacy to MM and benefit the military and Veteran populations.	*New research – no outcomes reported to date*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Blood Cancer				
CA140390 $561,600 Open	Reynaud/ Children's Hospital, Cincinnati	Investigating the Mechanisms of Leukemia Initiation in the Context of Obesity	RP: Obesity is a risk factor for leukemia, with an increase of incidence rate and poor outcome. This study is to test the hypothesis that the alteration of the adipokine signals associated with obesity may promote leukemia; specifically, this study will focus on the role of adiponectin and leptin on normal and leukemia-initiating hematopoietic stem cells. MR: As obesity is prevalent in the Veteran population, the link between obesity and blood cancers constitutes a concern for military personnel, Veterans, and their families. This work will provide an understanding of the mechanism between obesity and cancer, which could benefit the military and Veteran populations in the long run.	*New research – no outcomes reported to date*
CA140437 $525,600 Open	Qin/ Louisiana State University Health Sciences Center	HGF/c-MET Pathway in AIDS-Related Lymphoma	RP: The hypothesis is that hepatocyte growth factor (HGF)/ c-MET pathway mediates primary effusion lymphoma (PEL) pathogenesis. The study intends to elucidate mechanisms for the HGF/c-MET pathway controlling PEL survival and growth, and to identify how viral oncogenic proteins activate the HGF/c-MET pathway. MR: Military personnel who served overseas may have high risk factors for exposure to HIV/KSHV infection and potential to develop HIV/KSHV-related malignancies. PEL is a form of AIDS-related blood cancer.	*New research – no outcomes reported to date*
CA140783 $576,001 Open	Qin/ City of Hope Beckman Research Institute	Development of Antibody Therapy against Immunosuppressive Cells in Blood Cancer Patients	RP: To identify novel human myeloid-derived suppressor cell (MDSC)-specific markers and to develop novel strategies to inhibit MDSCs and treat blood cancers. MR: This study will benefit both Veterans and active duty military members who face the potential for higher risk for blood cancers and melanoma.	*New research – no outcomes reported to date*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Blood Cancer				
CA140945 $612,000 Open	Ngo/ City of Hope Beckman Research Institute	The Role of Cyclin D1 in the Chemoresistance of Mantle Cell Lymphoma	RP: To define the mechanisms underlying chemoresistance of mantle cell lymphoma (MCL). The hypothesis is that cyclin D1 (CCND1) regulates checkpoint kinase 1 (CHEK1) signaling to maintain cell survival and promote chemoresistance in TP53-deficient MCL by suppressing CCK5RAP3 expression. MR: Service members are at risk of developing blood cancers including lymphoma caused by exposure to chemical and biological agents. This study will facilitate development of therapies for MCL and thus will have a positive impact on Service members.	*New research – no outcomes reported to date*
Cancers Related to Radiation Exposure				
CA140307 $475,995 Open	Chao/ Duke University	A Novel Therapeutic Target for Radiation-Induced Hematological Malignancies: Calcium Calmodulin Kinase 2	RP: During Year 1, Dr. Chao determined that the kinase CaMKK2 plays an important role in the initiation and progression of lymphoma and myeloma. Additional studies indicated that when an inhibitor of CaMKK2 is administered after radiation exposure it appears to mitigate cancer development. Based on these results, Dr. Chao obtained a provisional patent for using CaMKK2 blockers as immune-modulators of the tumor microenvironment. MR: Although Veterans who participated in activities with radiation exposure during military service have a higher risk of developing blood cancer as they age, few drugs are approved to mitigate radiation injury.	*Patents: 1 (provisional)*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Cancers Related to Radiation Exposure				
CA140822 $448,502 Open	Natarajan/ University of Texas Health Science Center at San Antonio	Protein Interaction in Tissue Microenvironment Initiates the Onset of Cancer in Response to Occupational and Environmental Radiation Exposure	RP: During Year 1, Dr. Natarajan used an in vitro blood vessel model to demonstrate that the shear stress experienced by blood vessels combined with exposure to radiation increased oxidative stress as compared to controls that experienced neither shear stress nor radiation. MR: As Veterans or military personnel can have a higher risk for environmental or therapeutic radiation exposure, it is important to understand the mechanisms that drive tumor initiation and recurrence.	*None to date*
Colorectal Cancer (CRC)				
CA140515 $461,399 Open	Ellis/ University of Texas MD Anderson Cancer Center	Unbiased Screening for Identification of Effective Combination Therapies Targeting Oncogenic Pathways in Colorectal Cancer	RP: This study aims to develop a screen to test combinatorial therapies against CRC cells and assess the efficacy of these new drug combinations against patient-derived xerographs. The PI has developed an assay for screening drug effect on 3D cell cultures and that shows a significant difference in drug sensitivity between cells grown in a monolayer versus 3D culture. MR: CRC is the second leading cause of cancer death in the US, afflicting civilian and military populations alike. It is predicted that CRC alone will claim 50,000 lives this year.	*None to date*
CA140572 $576,000 Open	Park/ University of Texas MD Anderson Cancer Center	Dissecting TMEM9, a Wnt Signaling Regulator of Colorectal Cancer	RP: Study to determine the role of TMEM9 in intestinal tumorigenesis using mouse models and to evaluate cancer drugs in their ability to target TMEM9-regulated WNT signaling. In the first year of the award, the PI has confirmed that genetic ablation of TMEM9 in vivo is protective against tumorigenesis. I MR: Veterans are a high-risk population for exposure to known agents associated with human cancers. Novel therapeutics for such cancers including CRC, one of the most deadly of all cancers, would likely improve outcomes for this population.	*None*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Colorectal Cancer (CRC)				
CA140577 $310,000 Open	Gorham/ Naval Health Research Center	Serum 25-Hydroxyvitamin D and Subsequent Incidence of Colorectal Cancer in Active-Duty Personnel: A Nested Case-Control Study	RP: Study to quantify the relationship between 25-hydroxyvitamin D (25(OH)D) and incidence of CRC in active duty personnel. MR: This study will quantify prospectively the relationship between 25(OH)D in sera and CRC risk in active duty military, and provide information to indicate whether vitamin D may be useful in primary prevention of CRC. Primary prevention offers a further possibility of reducing incidence in the military.	*Publication: 1*
CA140616 $490,546 Open	Burnett-Hartman/ Kaiser Foundation Research Institute	The Association between Molecular Markers in Colorectal Sessile Serrated Polyps and Colorectal Cancer Risk	RP: A study to determine if there is a correlation between the histological characteristics of sessile serrated polyps (SSPs) and CRC risk in patients. Pathology review for 300 patient samples is underway and optimization of DNA methylation marker analysis is completed. MR: SSPs are associated with cigarette smoking, and cigarette smoking is associated with various cancers. Given that the prevalence of cigarette use in the military population is higher than in the general population, the utilization of SSPs as a new marker of CRC risk would be of greatest utility to the military population.	*Funding obtained: 3 grants*
CA140772 $466,500 Open	Messersmith/ University of Colorado Denver	Targeting the ALDH+ Tumorigenic Population in Colorectal Cancer	RP: This study will assess the effect of novel compound combinations that target WNT and NOTCH signaling pathways on tumor progression using patient-derived cells. Promising treatments will be validated against patient-derived xerographs. MR: CRC is the second leading cause of cancer death in the US. Exposure to ionizing radiation increases this cancer risk. New therapies for CRC would likely improve outcomes for military personnel, who are at higher risk due to radiation exposure while deployed.	*None*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Colorectal Cancer (CRC)				
CA140816 $538,480 Open	Levi/ Wake Forest University Health Sciences	Fluorescent Electrically Conductive Nanoparticles for Detection and Treatment of Metastatic Colorectal Cancer	RP: Develop targeted nanoparticles to CRC for photothermal ablation and demonstrate their efficacy in detecting chemotherapy-resistant cancer cells in a mouse model. PI has generated nanoparticles suitable for photothermal ablation and fluorescence detection in tissue. Work continues on functionalizing these nanoparticles for targeted delivery to the cancer site. MR: Metastasis is the main cause of CRC death. Given the high prevalence of CRC in both military and civilian populations, new treatments that would aid in preventing metastasis would greatly improve patient outcomes.	*Presentation: 1*
CA140882 $466,500 Open	Dakshanamurthy/ Georgetown University	Novel High-Fidelity Screening of Environmental Chemicals and Carcinogens and Mechanisms in Colorectal Cancer	RP: This project will identify the molecular targets and potential toxicity of environmental chemicals through in silico protein-chemical interaction mapping and intrinsic chemical properties. Biochemical validation and characterization of protein-chemical interaction will also be performed. The PI has screened in silico hundreds of environmental chemicals (EC) against thousands of potential proteins of interaction. The top 40 chemical-protein interactions were assigned as the "Tox-signature" for the ECs. Based on these signatures, compounds could be assigned to disease networks for which the predicted binding proteins belong. For biological validation, a subset of ECs previously predicted to perturb pathways with known importance in colorectal cancer was selected. Validation experiments are currently ongoing. MR: Environmental chemical exposure is an unavoidable risk of deployment and other operations. A better understanding of the molecular targets and toxicity of these agents will help to determine the relative cancer risk posed to military personnel and their families during service. .	*Publications: 4*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Colorectal Cancer (CRC)				
CA140948 $448,500 Open	Curiel/ University of Texas Health Science Center at San Antonio	Novel Listeria Vectors Secreting Gut Flora-Altering Agents to Prevent Colon Cancer and Treat Colitis	RP: Aims to modify the levels of B7-H1 expression within the gut using listeria as the modifying agent. Results from this work will help to determine a connection between B7-H1 mediated changes in the gut and reduced colon cancer risk. From the first year of the award, the PI has found that mice devoid of B7-H1 expression have a higher incidence of colon cancer and more severe colitis than wildtype mice. In the upcoming year, the PI will investigate whether increasing B7-H1 expression within the gut will be protective against colitis-associated colon cancer. MR: Colon inflammation increases one's risk of CRC. More than 35,000 cases of inflammatory bowel disease were identified in MHS beneficiaries within a single year. The development of methods to promote good gut health will help to mitigate the contribution of colitis to CRC risk	*None*
CA150370/P1/P2 $1,735,601 Open	Yeung; Pillarisetty/ University of Washington Tian/ Institute for Systems Biology	Tumor Slice Culture: A New Avatar in Personalized Oncology	RP: To establish a platform to interrogate drug sensitivity and to correlate the results with clinical and molecular data. Cytotoxic chemotherapy, targeted kinase inhibitors, and immunotherapy will be tested on patient-derived tumor slice cultures of CRC liver metastases. MR: Military Service members are exposed to various chemicals, biologics, and environments distinct from civilian exposure, which may result in cancer that exhibits distinctive biology or response to treatment. A personalized approach to treatment selection is therefore highly desirable.	*New research – no outcomes reported to date*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Colorectal Cancer (CRC)				
CA150494 $534,985 Open	Wei/ University of Kentucky	Targeting Sulfiredoxin in Colorectal Cancer	RP: Understand the mechanisms by which Sulfiredoxin (Srx), a protein that contributes to oxidative stress resistance, activates oncogenic signaling to promote CRC cell malignancy. Cell culture experiments and mouse xenograft models will be used to interrogate the functional role of Srx in CRC development. MR: Due to risk factors such as post-mission stress, environmental exposure, and genetic susceptibility, the incidence of CRC in Veterans is very high and ranked as the third most commonly diagnosed cancer. Nearly 50% of patients initially diagnosed with CRC will develop distal metastases, and the 5-year survival rate of patients with metastasis is only 6%	*New research – no outcomes reported to date*
CA150582 $607,999 Open	Moriarity/ University of Minnesota Twin Cities	Targeted Therapy Combined with Immune Modulation Using Gold Nanoparticles for Treating Metastatic Colorectal Cancer	RP: Generate gold nanoparticles (AuNPs) to systemically deliver a combinatorial therapy of immunogenic peptides and oncogene inhibitors. The utility of the AuNPs will be assessed in vivo for a mouse model of CRC. MR: Roughly 5% of all military personnel will develop CRC. Further, it has been postulated that young military personnel, due to their exposure to infectious agents in foreign countries, may be at higher risk for developing gastrointestinal diseases (irritable bowel disease, Crohn's disease, and CRC) later in life	*New research – no outcomes reported to date*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Colorectal Cancer (CRC)				
CA150595 $569,636 Open	Viswanath/ Case Western Reserve University	MRI-Pathology Correlation for Image Analytics-Based Treatment Outcome Assessment and Margin Planning in Rectal Cancers	RP: To develop novel computerized tools that utilize post-treatment MRI data to provide clinically actionable information about surgical treatment and its predicted benefit. Two new tools for colon cancer treatment outcome assessment will be developed and validated against patient data from university hospitals as well as the Cleveland VA Medical Center. MR: CRC is the third most frequently occurring cancer in the military, occurring in up to 8% of Veterans and 5% of active duty personnel. Over 75% of these patients will receive neoadjuvant chemoradiation therapy and would benefit from the tools developed in this project.	*New research – no outcomes reported to date*
CA150731 $130,751 Open	Gokare/ Institute for Cancer Research	Modulation of Therapeutic Response and Pharmacokinetics of 5-FU by P53 through Repression of the Pyrimidine Catabolic Gene Dihydropyrimidine Dehydrogenase (DPYD)	RP: A study to assess the role of p53 mutations in the alteration of metabolism and therapeutic sensitivity of 5-Fluorouracil (5-FU), the major component of CRC chemotherapy. Will use a combination of cancer cell lines and transgenic mice with known mutations in the p52 tumor suppressor gene and assess expression level difference of 5-FU metabolic protein, DPYD, as well as cell proliferation and viability in the presence of the chemotherapeutic agent. MR: CRC is the third most frequently occurring cancer in the Veteran and military populations, occurring in up to 8% of Veterans and 5% of active duty personnel.	*New research – no outcomes reported to date*
CA150808 $125,250 Open	Tosti/ Albert Einstein College of Medicine	The Role of Mismatch Repair and Microbiome in Inflammation-Associated Colon Cancer	RP: A study to investigate the relationship between TGFBRII inactivation and the colonic microbiota in DNA mismatch repair (MMR)-driven tumorigenesis. This study will investigate the differences in survival, tumor incidence/location, and histopathology of MMR-impaired mice and examine the impact on colon tumorigenesis upon intestinal microbiota alteration within these mice. MR: CRC represents the third most common cancer type worldwide. Genetic instability is a major cause in the initiation and progression of CRC and DNA MMR is essential to preserve genome integrity and suppress tumorigenesis.	*New research – no outcomes reported to date*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Colorectal Cancer (CRC)				
CA150873 $127,125 Open	Sauer/ New York University School of Medicine	Structure and Function of the Reduced Folate Carrier	RP: A project to solve the 3D crystal structure of the human Reduced Folate Carrier (hRFC) protein. Folates play an important role in cell metabolism and limitations in cellular folate levels or defects in the folate cycle have been linked to cancer. The project will provide fundamental information on the structure of the protein and a basis for future rational drug design. MR: A structural description of hRFC is necessary for structure-based drug design of novel chemotherapeutics acting on the folate pathway. This work will directly benefit Service members, their families, and beneficiaries by accelerating the development of new chemotherapies.	*New research – no outcomes reported to date*
CA150899 $113,625 Open	Carpenter/ St. Louis University	Colorectal Cancer Immunotherapy by Pharmacological Suppression of Liver X Receptor Activity	RP: To investigate the role of liver X receptor (LXR) activation in the process of immune evasion by tumor cells. The study will determine whether blocking the receptor/ligand interaction of activating signals released by tumors is sufficient to stimulate T-cell response to CRC cells in vitro. Additional experiments will test the efficiency of these blocking agents to treat CRC in mice. MR: There are approximately one million new cases of CRC worldwide per year; it is the third most diagnosed cancer within the VA system. The identification of novel treatments for CRC is therefore relevant to the health and well-being of military personnel and their beneficiaries.	*New research – no outcomes reported to date*
CA150908 $108,000 Open	Gomez/ University of Kansas Center for Research, Inc.	A Role for APC in Goblet Cell Function and the Unfolded Protein Response	RP: To determine the regulation, role, and function of the tumor suppressor Adenomatous Polyposis Coli (APC) in unfolded protein response (UPR) within colon cancer cell line. Will also investigate the effect of chemical stimulation of UPR on APC levels and inflammation using mice with induced colitis. MR: Approximately 10%-15% of inflammatory bowel disease patients die from CRC. According to the American Cancer Society, ~50,000 people will die from CRC in 2015. Currently, in the United States, CRC is the second leading cause of cancer-related deaths in both men and women combined.	*New research – no outcomes reported to date*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Colorectal Cancer (CRC)				
CA160344/P1 $1,290,329 Open	Frank/ Boston VA Research Institute, Inc. (BVARI) Lian/ Brigham and Women's Hospital	Targeting Therapeutic Resistance in Colorectal Cancer	RP: While promising new CRC therapies show improvement in patient survival, the long-term success of these treatments is limited by the emergence of cancer resistance. This project will examine whether expression levels of known multidrug resistance mediator ABCB5 correlate to clinical outcomes in patients treated with CRC targeted therapies. Additionally, the research team will also investigate whether blocking ABCB5 can improve the longevity of these therapies in preclinical models. Work on this project has just initiated. MR: CRC is a disease caused by exposure to ionizing radiation during service. It is also one of the major causes of morbidity and mortality among military Veterans. Thus, identification and selective targeting of drug resistance mechanisms is of major importance for the long-term success of treatments for clinical disease.	*Research initiated*
CA160741 $553,,635 Open	Kim/ Yale University	Improving Immunotherapy: Boosting Immune Response and Functional Immune Cell Imaging	RP: This project aims to determine whether thermal ablation and immune checkpoint blockers can synergize their therapeutic effect when applied in combination within a mouse model of CRC. The PI will also develop novel imaging tools that have the potential to monitor immune response in real time using non-invasive techniques. Work on this project has just initiated. MR: CRC is the third most common form of cancer among active duty personnel and Veterans. Up to 50% of patients present with or develop distant metastases limiting 5-year survival to 13% if unresectable. Thus, more effective treatment strategies to improve outcomes of patients with advanced CRC are highly warranted.	*Research initiated*
CA160988 $192,966 Open	Malaby/ University of Vermont	Mechanisms of Selective Susceptibility to Inhibition of a Cytoskeletal Regulator in Colorectal Cancer Cells	RP: This project aims to characterize the effect of Kif18A depletion within multiple colorectal cancer cell lines. Kif18A is a motor protein associated with increased colorectal cancer metastasis and poor prognosis. Work on this project has just initiated. MR: Statistics show that CRC is the second most deadly cancer for Service members.	*Research initiated*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Colorectal Cancer (CRC)				
CA161001 $247,500 Open	Mahara/ Monash University	Therapeutic Targeting of CIMP+ Colorectal Cancers	RP: This project will investigate whether small molecules that target the function of enzymes responsible for epigenetic modification can be used to rescue the function of previously inactivated tumor suppressor genes. Work on this project has just initiated. MR: Frequent exposure to cancer-associated agents places the US military population at higher risk for CRC.	*Research initiated*
Genetic Cancer				
CA100865/P1/P2 $1,085,960 Open	Alvarez; Couto; Huang/ 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 infrastructure, statistical method for analyzing genetic data, and military dog registry database are established. Collection of blood samples and health records for the military working dogs has been initiated, and analysis is in progress. 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.	*Publications: 3* *Presentations: 7*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Genetic Cancer				
CA140196 $446,542 Open	Walkley/ St. Vincent's Institute of Medical Research	How Does a DNA Helicase Regulate Blood Cell Development and Disease?	RP: Goal is to understand role of the DNA helicase, RECQL4, in regulating hematopoiesis and the development of blood cancer. Early results indicate that mutations in Recql4 cause different effects depending on the amount of the protein remaining. Very short fragments are not able to keep cells alive, but larger protein fragments, including those with mutations that prevent helicase activity, are able to support cell proliferation. The PI is currently testing these cells to determine how they respond to stressors such as radiation and chemotherapy. MR: The military population can be disproportionately exposed to DNA-damaging agents or carcinogenic chemicals such as chemical weapons or solvents associated with occupational tasks. Thus, it is important to understand how these agents may lead to disease.	*Presentation : 1* *Funding Obtained: 1*
CA140303 $569,841 Open	Moldovan/ Pennsylvania State University	The PCNA-PARI Pathway of Genome Stability in Cancer	RP: Test the hypothesis that the protein PARI promotes leukemia by blocking DNA damage-induced differentiation, and determine whether PARI inhibition of NF-kB activation promotes leukemic differentiation. Year 1 results show cells with reduced PARI exhibit increased leukemic differentiation, arrested proliferation, and increased apoptosis. This correlates with increased spontaneous replication stress and DNA damage, and confirms the model that PARI inhibits differentiation through suppression of replication stress. The underlying mechanism involves NFκB increasing p21 gene expression, resulting in proliferation arrest and induction of differentiation. MR: Radiation exposure is a well-known, militarily relevant risk factor. Radiation creates DNA damage; in particular, radiation exposure results in increased incidence of leukemia. This research investigates a new pathway that repairs radiation-induced DNA damage and explores its impact on leukemia development and treatment.	*Presentation: 1*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Genetic Cancer				
CA140321 $528,000 Open	MacPherson/ Fred Hutchinson Cancer Research Center	Developing a KMT2D/MLL2-Deleted Preclinical Mouse Model of Bladder Urothelial Cancer	RP: Develop a mouse model of bladder cancer that exhibits several bladder cancer markers, and test a new hypothesis for treating bladder cancer. PI completed the necessary mouse crosses and genotyped a panel of bladder cancer cells lines to set up more in-depth mechanistic studies during year two.. MR: Smoking is a risk factor for bladder cancer. Use of tobacco products occurs at higher rates in active military than the general population and is particularly high in deployed military. This work has potential to improve survival rates in military personnel and their families who develop bladder cancer.	*None to date*
CA150188 $708,000 Open	Cantor/ Children's Hospital Boston	Genetic Risk Factors for Clonal Hematopoiesis and Leukemia Development Following Ionizing Radiation and Chemical Exposure	RP: To determine if pre-existing genetic mutations within members of the DNA damage response (DDR) pathway leads to a selective advantage for cells within the bone marrow that are pre-disposed to genomic instability upon low-level ionizing radiation. Mice deficient in specific DDR members will be used to evaluate this effect in vivo. MR: This proposal is directly relevant to members of the Armed Forces and their families because of their increased risk of exposure to ionizing radiation and DNA-damaging chemicals, particularly in the age of global terrorism.	*New research – no outcomes reported to date*
CA150414 $606,975 Open	Magnuson/ University of North Carolina at Chapel Hill	Co-Occurrent Mutations in Chromatin Regulators Define Genetically Distinct Forms of Cancer	RP: To create a pipeline to prioritize mutations commonly found in hepatocellular carcinoma, characterize their effect on tumorigenesis in vitro and in vivo, and identify genes that are synthetically lethal with each new model. Linking data on co-occurring somatic mutation rates with new genome-editing techniques will allow for analysis of many more combinations of mutations than is currently common. The long-term goal of the study is to increase the speed of identifying novel therapeutic targets based on the genetics of specific tumors. MR: Liver cancer is particularly prevalent among Veterans who served from 1945-1965. The high mortality rate associated with liver cancer makes linking the mutations of the disease to new therapeutic targets a pressing need for this population.	*New research – no outcomes reported to date*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Genetic Cancer				
CA150794 $127,125 Open	Daniloski/ New York University School of Medicine	Elucidate the Mechanism of Telomere Maintenance in STAG2 Mutated Tumor Cells	RP: To test the hypothesis that STAG2 mutated tumors utilize both telomerase and ALT to elongate their telomeres and that forced resolution of the persistent telomere cohesion will lead to rapid cancer cell death. MR: Due to exposure to ionizing radiation, chemicals, and environmental carcinogens, military personnel are at particularly high risk for DNA damage that can lead to increased gene mutations and promote cancer formation. This study addresses how tumors carrying mutations in STAG2 gene maintain their telomeres.	*New research – no outcomes reported to date*
CA150795 $128,550 Open	Ghisays/ Memorial Sloan Kettering Cancer Center	RTEL1 and Genome Stability	RP: To examine the functions of RTEL1 in cells and in a mouse model to better understand role of genome stability in the development and aging of proliferative tissues and tumor suppression. MR: Both myeloid proliferative disorders, and cancer, are diseases affecting Service members, their families, and the general population; a complete understanding of initiation and progression of these diseases remains unknown. Characterization of RTEL1 biology in the context of the myeloid proliferative disorders and cancer development will provide unique insights that can be immediately translated into clinical care.	*New research – no outcomes reported to date*
CA150827 $108,350 Open	Roberts/ Northwestern University	Cobalt(III) Schiff Base Complexes as Inhibitors of p53 Aggregation in Cancer	RP: Recent research indicates that aggregation of mutant p53 leads to a dominant negative effect on any wild-type p53 that may be remaining in tumor cells. The PI proposes to design and synthesize Cobalt (III) Schiff Bases that target mutant p53 and prevent aggregation. MR: Mutations in p53 are the most common clinically observed cancer causing mutations and present in over 50% of all cancers. The development of a novel therapeutic would benefit Service members, Veterans, and military beneficiaries who are affected by cancers containing p53 mutations.	*New research – no outcomes reported to date*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Genetic Cancer				
CA150844 $80,370 Open	Wadugu/ Washington University	The Role of Mutant U2Af1 in the Pathogenesis of Myelodysplastic Syndromes	RP: The PI will create a novel mouse model of myelodysplastic syndrome (MDS) to determine if and how two mutations that often co-occur in the same tumor, U2AF1 and ASXL1, lead to tumorigenesis. MR: Identifying genetic mutations contributing to MDS initiation is key to developing effective prognostic and therapeutic strategies. The mouse models used here will be valuable reagents for the research community to test drugs in future preclinical studies.	*New research – no outcomes reported to date*
CA150882 $125,694 Open	Hsieh/ Cornell University Weill Medical College	Characterization of Ran Binding Protein (RANBP6) as Candidate Tumor Suppressor	RP: To test the hypothesis that the tumor suppressor function of ran binding protein 6 (RanBP6) stems from its role as regulator of nuclear import/export. The PI will identify RanBP6 substrates, characterize RanBP6 mutations that are common in multiple types of cancer, and explore the tumor suppressor activity of RanBP6 in a murine pancreatic organoid model. MR: These studies aim to broaden the currently rudimentary knowledge on how Ran and Ran binding proteins contribute to tumorigenesis and will provide new opportunities to therapeutically target deregulated growth factor signaling in cancer, which will not only benefit the military families but also the Service members and Veterans, who have an increased risk of developing cancer due to a higher chance of exposure to carcinogens.	*New research – no outcomes reported to date*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Immunotherapy				
CA160022 $633,771 Open	de Gracia Lux/ University of Texas Southwestern Medical Center at Dallas	Eliminating Ex Vivo Manipulation and Viral Transfection of T Cells in CAR T-Cell Immunotherapy of B-Cell Malignancies Using Ultrasound-Based Gene Delivery	RP: This project will optimize conditions for T-cell targeted ultrasound mediated gene transfection for use as a new chimeric antigen receptor (CAR) T-cell immunotherapy. The transfection method will be tested in vitro and in vivo for function and efficiency of B-cell depletion. Work on this project has just initiated. MR: Childhood malignancies are devastating to families that watch their child suffer and potentially succumb to their disease. It also creates stress and financial and time costs on caregivers, especially if the parent is an active military member with time commitments away from home.	*Research initiated*
CA160218 $399,723 Open	Zhao/ University of California, Irvine	Context-Dependent CAR Activation: Engineering Mechanosensitive T Cells to Treat Solid Tumor Metastases	RP: Project to reduce the off-target effects of CAR-T cell therapy by developing CAR-T cells that activate only in the presence of tumor microenvironment signals. The PI will design and test the new therapy for in vitro and in vivo functionality, tumor-killing efficiency, and on target activation. Work on this project has just initiated. MR: Developing new CAR-T cell therapy to treat metastatic colorectal cancer will potentially benefit military beneficiaries as colorectal cancer incidence rate is skewed towards current Veterans due to age and exposure related risks.	*Research initiated*
CA160315 $568,800 Open	Luke/ The University of Chicago	Genomic and Commensal Variants Associated with Immunotherapy in Cancer Patients	RP: Immune cell infiltration in tumors is necessary for tumor clearance. This project will identify factors that may lead to exclusion of immune cells from the tumor. The PI will compare somatic, germline, and microbiota differences among patients to determine what changes correlate with clinical outcomes, T-cell presence in and around tumors, and response to immunotherapy. Work on this project has just initiated. MR: Cancer is among the most common chronic diseases experienced by military Veterans and active duty Service members. By identifying genomic and environmental molecular mechanisms influencing cancer immunotherapy this research could improve treatment options for military-associated persons.	*Research initiated*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Immunotherapy				
CA160356 $566,284 Open	Viapiano/ State University of New York Upstate Medical University	Engineering T Cells Against the Tumor Extracellular Matrix for Enhanced Immunotherapy of Mesothelioma	RP: Aims to determine whether Chimeric Antigen Receptor-expressing T cells targeted to the extracellular matrix of solid tumors could be used as effective therapy for malignant mesotheliomas (MM). The PI will engineer these new cytotoxic T cells and evaluate their specificity and efficacy in xenograft mouse models of mesothelioma. Work on this project has just initiated. MR: The major cause of MM is chronic exposure to asbestos, which was a common occurrence in US military installations until the late 1970s, and is still a respiratory risk in combat and disaster zones in countries that have not banned asbestos use.	*Research initiated*
CA160396 $612,000 Open	Gumperz/ University of Wisconsin at Madison	Modeling Human Gamma Delta T Cells as Antitumor Agents In Vivo	RP: Will determine what signals are required for a subset of poorly characterized T cells, the gamma-delta positive T cells, to control human lymphomas. Using engineered mice, the PI will administer gamma-delta positive T cells in the absence or presence of drugs that affect various aspects of T cell physiology and observe their influence on tumor burden in these mice. Work on this project has just initiated. MR: Exposure to militarily relevant chemical mutagens (e.g., Agent Orange) and ionizing radiation has been found to be associated with increased risk of developing B cell lymphomas. Novel treatments of this disease would therefore have a major impact on military personnel and their families.	*Research initiated*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Immunotherapy				
CA160461/P1/P2 $1,579,875 Open	Lee/ Research Institute at Nationwide Children's Hospital Cairo/ New York Medical College Seeger/ Children's Hospital, Los Angeles	Overcoming Immune Escape Mechanisms in Immunotherapy of Neuroblastoma	RP: The two major aims of this study are (1) correlate persistence, phenotype, and anti-neuroblastoma function of activated NK cells to clinical outcomes of the NANT-2013 clinical trial, and (2) identify clinically translatable modifications to tumor microenvironment to improve the clinical outcomes of the current NB immunotherapy platform. MR: This proposal addresses childhood neuroblastoma, the most common extracranial solid tumor in children and one that, by means of its poor survival, high morbidity, and protracted course has a disproportionate effect on parents, including those in the military.	*Research initiated*
CA160480 $568,800 Open	Hsu/ University of Virginia	Diacylglycerol Activation of T-Cell Receptor Signaling for Cancer Immunotherapy	RP: This project will investigate whether manipulation of lipid metabolism and signaling can enhance patient immune response to melanoma. The PI will target an important lipid modifying protein, DAGK, to determine whether inhibition of this protein by the drug ritanserin can influence melanoma clearance in vitro and in vivo. Work on this project has just initiated. MR: Immunotherapy shows great promise for a wide range of cancers and can offer breakthrough treatment options for Service members and their families. This study will focus on melanoma, which has been shown to have a higher incidence in US military population than in the general population according to the Automated Central Tumor Registry published by DoD.	*Research initiated*
CA160503 $644,894 Open	Wang/ University of Southern California	Engineering of Tumor-Selective CAR for Adoptive Cell Therapy Against Kidney Cancer	RP: The PI proposes developing and testing a new chimeric antigen receptor (CAR) that will be capable of reducing on-target, off-tumor adverse effects associated with kidney cancer immunotherapies. MR: Veterans who participated in radiation risk activities are at higher risk for cancers of the urinary tract, including renal cell carcinoma (RCC).	*Research initiated*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Immunotherapy				
CA160591 $531,700 Open	Varadarajan/ University of Houston	Balancing T-Cell Function and Metabolism for Immunotherapy	RP: This project aims to develop a molecular sensor that will enable researchers to directly monitor metabolism on the single cell level. The PI will use human T cells expressing this sensor to monitor the dynamic metabolic changes that occur in T cells when cultured in low glucose conditions ex vivo or while present in nutrient-poor environments such as the tumor microenvironment. Work on this project has just initiated. MR: The most recent and comprehensive study comparing the military versus the NCI Surveillance, Epidemiology, and End Results Program (SEER) demonstrated that the overall melanoma incidence rate in active duty military personnel was 62% greater than the general SEER population between 2000-2007.	*Research initiated*
CA160714/P1/P2 $1,585,744 Open	Conforti; Wise-Draper/ University of Cincinnati Janssen/ Children's Hospital, Cincinnati	Ionic Mechanisms of Resistance to Immunotherapy in Head and Neck Cancer	RP: The objective is to understand why immunotherapy works in some people and does not work in others. Focusing on the response or resistance to anti-PD1 therapy in head and neck squamous cell carcinoma patients, the team will investigate whether proteins that regulate calcium and potassium signaling within immune cells could account for these differences in drug response. Work on this project has just initiated. MR: 400,000 new head and neck squamous cell carcinoma (HNSCC) cases are diagnosed each year with an overall 5-year survival rate of less than 50% for high-risk cases. Veterans have twice the prevalence of HNSCC compared to non-Veterans.	*Research initiated*
CA160938 $231,656 Open	Shakiba/ Memorial Sloan Kettering Cancer Center	The Impact of TCR Affinity on T-Cell Dysfunction and Immunotherapeutic Reprogramming in Solid Tumors	RP: The PI plans to examine if the affinity of the cell-to-cell interaction between a T cell and its target cell plays a role in the induction of T-cell dysfunction. Using engineered T cells with distinct affinities, the PI will examine the underlying cellular and molecular differences in T cells encountering low- vs. high-affinity tumor antigens. MR: This work will provide important insights into regulatory mechanisms of T-cell dysfunction in tumors, potentially leading to strategies for novel cancer immunotherapies.	*Research initiated*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Immunotherapy				
CA161007 $236,627 Open	Pituch/ Northwestern University	Combination of IL13Ralpha2 CAR T-Cell Therapy with PD-1 Immune Checkpoint Blockade for Treatment of Glioblastoma	RP: Determine the central mechanisms (1) regulating CAR-T cell homeostasis at the glioblastoma multiforme (GBM) tumor site, (2) regulating infiltration into the GBM mass, and (3) of PD-1 mediated regulation of IL13Ra2-CAR T cell activity in immune competent mouse models of GBM. MR: GBM is an aggressive type of brain tumor; most people diagnosed are between the ages of 45 and 70, and the majority of those diagnosed are men, demographics that also strongly coincide with our Veteran population.	*Research initiated*
Kidney Cancer				
CA100606/P1 $1,206,215 Open	Tewari/ Fred Hutchinson Cancer Research Center Pantuck/ 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. Initially optimized the detection method for miR-210. Demonstrated that miR-210 was elevated in renal carcinoma serum samples. Identified seven additional miRNAs as potential serum biomarkers, which will be further examined along with miR-210. 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.	*Publication: 2*
CA120297 $364,353 Open	Krishnan/ 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 determine if inhibition of these kinases improves the responsiveness of mTOR inhibitors in renal cell carcinoma. To date, the PI has found that the combination therapy of Dasatinib/Everolimus overcomes the acquired resistance to Everolimus alone in a PDX model of renal cell carcinoma (RCC). Additional studies explore the use of other kinase inhibitors to use in combination with Everolimus. MR: This study could potentially improve the outcomes and survival of military personnel with RCC.	*Publication: 1* *Presentation: 1* *Funding Obtained: 1*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Kidney Cancer				
CA130028 $474,562 Open	Czyzyk-Krzeska/ University of Cincinnati	Effects of Tobacco Smoke (TS) on Growth of Clear Cell Renal Cell Carcinoma (ccRCC)	RP: To identify somatic mutations in DNA extracted from clear cell renal cell carcinoma (ccRCC) tumors from male Veterans and heavy smokers as compared to matched ccRCC patient non-smokers and identify gene expression profiles. Early results indicate that smokers tend to exhibit more deleterious mutations than non-smokers. In particular, mutations in the promoter of the VHL gene are more detrimental in smokers than non-smokers. MR: There is a high prevalence of smoking in male active duty military personnel and Veterans along with a higher rate of kidney cancer than in those who are non-military.	*None to date*
CA130458 $602,996 Open	Ebos/ Health Research Inc., Roswell Park Division	Distinguishing Tumor- and Stromal-Mediated Mechanisms of Resistance and Rebound in Models of Metastatic Renal Cell Carcinoma	RP: Investigate the role of tumor and stromal reactions to antiangiogenic therapy in RCC mouse models. To date, the PI has identified multiple pathways that may be important in tumors developing therapeutic resistance. Current studies seek to elaborate on the mechanisms driving these putative resistance pathways. MR: Service members have higher risk for developing kidney cancer because of deployment-related exposure to environment hazards.	*Publications: 3 reviews* *Presentations: 9*
CA140443 $547,200 Open	Zhang/ University of North Carolina at Chapel Hill	Validation of ZHX2 as a Novel pVHL E3 Ligase Substrate and Its Role in Kidney Cancer	RP: Confirm that zinc finger homeobox protein 2 (ZHX2) levels are negatively regulated by the tumor suppressor pVHL, and determine the functional relevance of ZHX2 in renal cell carcinogenesis. MR: The proposed work can have potentially significant impact on military beneficiaries because (1) smoking cigarettes, which 30% of active duty personnel do, is a significant risk factor for RCC and (2) occupational exposure to heavy metals, paints, organic solvents, and other combat-related chemicals significantly increases the risk of RCC.	*New research – no outcomes reported to date*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Kidney Cancer				
CA140497 $585,000 Open	Sabatini/ Whitehead Institute for Biomedical Research	Role of Lysosomal Transporters in Promoting the Growth of Clear Cell Renal Cell Carcinoma and Other Tumor Types	RP: Developed a lysosomal IP-LC/MS method and used it to characterize the role of a transporter protein, SLC38A9, in arginine-mediated mTORC1 activation. PI also identified another lysosomal transporter, ABCC10, for follow-up in kidney cancer cell lines in vitro and in vivo. These studies are uncovering the role of lysosomal metabolites and transporters in nutrient-mediated mTORC1 activation in kidney cancer. MR: The leading risk factors for clear cell renal cell carcinoma (ccRCC) are smoking, hypertension, and chronic kidney dialysis, all of which are more prevalent among military beneficiaries than in the general population. The proposed research will provide the basis for developing new anti-cancer drugs to improve therapeutic options and decrease the burden of ccRCC on the military healthcare system.	*Publication: 1*
CA140917 $486,000 Open	Hammers/ University of Texas Southwestern	Enhancing Immune Checkpoint Inhibitor Therapy in Kidney Cancer	RP: Test the hypothesis that patient responses to immune checkpoint inhibitors will be improved by auto-vaccination approaches, and that these approaches will synergize with other immune-targeting therapies. The PI recently transferred to a new institution and is just initiating work on this award. MR: Service members have higher risk for developing kidney cancer because of deployment-related exposure to environment hazards.	*None to date*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Kidney Cancer				
CA150289 $779,349 Open	Rastinejad/ Sanford-Burnham Medical Research Institute, Orlando	Novel Hypoxia-Directed Cancer Therapeutics	RP: Test the hypothesis that the ligand binding pockets of HIF-1α/ARNT and HIF-2α/ARNT can be targeted for drug discovery through small molecule inhibitors. The short-term objectives are to identify diverse novel small molecule inhibitors for each of HIF-1α and HIF-2α proteins using high-throughput screening and cell culture functional characterization. The long-term goals are to advance the inhibitors as preclinical anti-cancer drugs through synthetic medicinal chemistry, pharmacology, and animal studies. MR: HIF-targeted drugs can broadly impact both civilian and military personnel suffering from advanced cancers. The new treatment options that may ultimately emerge from this research would benefit patients with a variety of cancers that are currently resistant to existing treatments.	*New research – no outcomes reported to date*
CA150395 $569,236 Open	Leppert/ Stanford University	IQGAP1 Scaffold-Kinase Interaction Blockade in Renal Cell Carcinoma: A Novel Biomarker and Therapeutic Strategy	RP: The intracellular scaffold protein IQGAP1 is required for ERK1/2-driven tumor progression. The PI will evaluate IQGAP1 expression in renal cell carcinoma (RCC) tumors, and correlate this to RAS signaling, the signaling pathway that involves ERK1/2, and clinical outcomes. Additionally, the PI will study IQGAP1 inhibitors in tissue slice cultures and patient-derived xenograft models. MR: Veterans and military beneficiaries represent a highly relevant population at risk of RCC due to male predominance of RCC, the increasing age of the military beneficiary population, and potential environmental and medical conditions associated with RCC. As a result, RCC is the fourth most common solid tumor diagnosed among military beneficiaries receiving care in the Veterans Health Administration.	*New research – no outcomes reported to date*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Kidney Cancer				
CA160279 $597,600 Open	Ho/ Mayo Clinic and Foundation, Scottsdale	Reprogramming Chromatin Modifiers in Kidney Cancer	RP: The PI hopes to improve upon treatments in metastatic RCC and identify patients with small renal tumors with an unexpected higher risk of recurrence by elucidating the role of chromatin modifications in RCC, and to test whether DNA hypermethylation represents a reversible, druggable mechanism. MR: RCC preferentially affects males, the predominant gender of the Armed Forces, and is associated with an average of 12 years of lost life. Therefore, improved ability to detect those who are most likely to experience RCC recurrence would be beneficial to members of the military and their beneficiaries.	*Research initiated*
CA160448 $540,506 Open	Dykhuizen/ Purdue University	Bromodomain Targeting of PBRM1, a P-BAF Chromatin Remodeling Complex Subunit Highly Mutated in Kidney Cancer	RP: The overall objective of this study is to define how PBRM1 is targeted to cell adhesion genes, and define how this is related to PBRM1's role in tumor progression, metastasis and response to targeted therapies. MR: Clear cell renal cell carcinoma (ccRCC) is the most common and lethal type of kidney cancer in adults, with increased incidence in military populations. Even with the advent of targeted therapies, the survival rate for metastatic renal carcinoma is still only 22 months.	*New research – no outcomes reported to date*
CA160728/P1/P2 $1,590,907 Open	Jonasch/ The University of Texas MD Anderson Cancer Center Rathmell; Haake/ Vanderbilt University Medical Center	Prognostic and Predictive Markers of Immunogenicity in Renal Cell Carcinoma	RP: The PIs will use renal cell carcinoma (RCC) samples collected from multiple trials, including one VA trial, to assess: (1) whether certain chromatin remodeling mutations ultimately influences T cell tumor infiltration, and to determine if the genomic background of the tumor can be correlated to clinical trial outcomes; (2) whether treatment with antiangiogenic agents enhances patient response to checkpoint antibody therapy. Additionally, the PIs will conduct preclinical studies to better ascertain how specific mutations effect the tumor microenvironment in response to anti-PD1 therapy. MR: RCC is a disease associated with male gender, increasing age, smoking, obesity, and hypertension, all factors prevalent in members of the Military. The predictive biomarkers developed in this grant will fundamentally alter the approach we take to treatment of military patients with advanced RCC.	*Research initiated*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Listeria Vaccine for Cancer				
CA160681 $567,969 Open	Snook/ Thomas Jefferson University	Metastatic Colorectal Cancer Immunotherapy with GUCY2C-Expressing Listeria monocytogenes	RP: Employ mouse models to test the hypothesis that modified listeria-based vaccines are superior to current technologies when used as immunotherapeutics for the treatment of colorectal cancer. The PI will perform in vivo efficacy and safety studies for newly developed listeria-based vaccines. Work on this project has just initiated. MR: Colorectal cancer (CRC) is the fourth most common neoplasm with ~150,000 new cases/year, and the second leading cause of cancer mortality, in civilians and the military, with a mortality of ~50%. The military has a unique increased burden for this disease at a younger age (<50 yo), and these patients present with advanced disease, which is more likely to recur.	*Research initiated*
Liver Cancer				
CA150178 $610,200 Open	Lujambio/ Icahn School of Medicine at Mount Sinai	Functional Genomics Screen for Combination Therapy Discovery in Liver Cancer	RP: A study to develop new combinatorial therapies for hepatocellular carcinoma that increase the efficacy of palbaciclib, a Food and Drug Administration (FDA)-approved cancer treatment. Will use a molecular knockdown approach to identify genes and pathways that regulate palbaciclib activity. MR: The incidence of hepatocellular carcinoma (HCC) is increasing in the United States, especially within the US Military and Veterans communities. Most of the main risk factors for HCC, such as alcohol consumption, hepatitis B and C infection, obesity, and male gender, are over-represented within the US Military and Veterans communities.	*New research – no outcomes reported to date*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Liver Cancer				
CA150245/P1/ P2/P3/P4 $1,818,164 Open	Zhu; Yopp; Singal; Siegwart/ University of Texas Southwestern Medical Center at Dallas Waljee/ University of Michigan	Defining Hepatocellular Carcinoma Subtypes and Treatment Responses in Patient-Derived Tumorgrafts	RP: A study to better understand the basic biology of hepatocellular carcinoma (HCC) at different disease stages. Using patient-derived xenografts, the molecular signature of these cancers will be established, and their susceptibility to small RNA therapies will be investigated. The patient-derived xenografts will also be examined for their utility to identify prognostic biomarkers for small molecule sensitivity. MR: The military population is particularly vulnerable to HCC, given higher rates of hepatitis C virus (HCV) infection, obesity, diabetes, and alcohol abuse than the general population. Over the last 10 years, HCC incidence has more than tripled among US Veterans.	*New research – no outcomes reported to date*
CA150248 $613,200 Open	Lau/ Northern California Institute for Research and Education	The Genetic Basis of Sex Differences in Liver Cancer	RP: To validate a male-specific cancer gene, TSPY, as a diagnostic and predictive marker in liver cancer. Will establish the contribution of TSPY and other Y chromosome-expressed genes to liver cancer pathology. MR: Risk factors pertaining to liver cancer are most prevalent among military members and Veterans. The proposed research plans to validate TSPY as a diagnostic and predictive marker of liver cancer utilizing patients from VA Hospital San Francisco.	*New research – no outcomes reported to date*
CA150262 $438,152 Open	Albrecht/ VA Medical Center Minneapolis, MN	The Role of CDK2 in Hepatocellular Carcinoma	RP: Explore the mechanisms by which cell cycle regulator cdk2 contributes to hepatocellular carcinoma (HCC). Using a mouse model that is highly protected against HCC development, genes contributing to cdk2 pathology will be identified. MR: The proposed research is highly relevant to military Veterans because of the increasing incidence of HCC in this population.	*New research – no outcomes reported to date*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Liver Cancer				
CA150272/P1/ P2/P3/P4 $2,047,765 Open	Friedman; Llovet; Lujambo; Villanueva/ Icahn School of Medicine at Mount Sinai Lowe/ Memorial Sloan Kettering Cancer Center	Mechanisms of Acquired Resistance to Sorafenib in Hepatocellular Carcinoma	RP: Identify the critical elements of sorafenib resistance in hepatocellular carcinoma (HCC). Using a combination of patient-derived biopsies, 3D cultured organoids, and tumor stroma samples, the molecular mechanism of resistance will be investigated and second line drug targets will be identified and validated. MR: The incidence of HCC is increasing in the US, especially within the Military and Veterans communities. Among the main risk factors for HCC development are alcohol consumption, hepatitis B and C infection, obesity, and male gender, all of which are over-represented in the US Military and Veterans communities.	*New research – no outcomes reported to date*
CA150281 $664,359 Open	Hoshida/ Icahn School of Medicine at Mount Sinai	Gene Regulatory Networks as Targets and Biomarkers for Liver Cancer Chemoprevention after Clearance of Oncogenic Hepatitis C Virus	RP: To develop an experimental system that will enable identification of cancer prevention targets and biomarkers of liver cancer post- hepatitis C virus (HCV) clearance. A cell-based model will be used to describe molecular changes that occur as a result of oncogenic HCV. MR: The prevalence of HCV infection in US Veterans is more than threefold higher than in the US general population. The number of Veterans with HCV-related liver cancer has increased ninefold over the past decade.	*New research – no outcomes reported to date*
CA150480 $677,998 Open	Yu/ Icahn School of Medicine at Mount Sinai	Enhancing Efficacy of the PD-1/PD-L1 Inhibitor-Mediated Anti-Liver Cancer Immunotherapy through Promoting CD8+ T-Cell Infiltration by Targeting Angiopoietin-1	RP: Aims to develop a novel way to enhance therapeutic efficacy of FDA-approved immune checkpoint inhibitors against liver cancer. Will examine whether inhibition of Angpt1, a potential target of established oncogenes, will contribute to enhanced tumor clearance in mouse models of hepatic cancer. MR: Rates of liver cancer are on the rise in Western countries largely due to obesity and hepatitis C virus (HCV) infection as there is no vaccine against HCV. Military personnel have an increased chance of virus infection during deployment and combat and are at higher risk of developing liver cancer.	*New research – no outcomes reported to date*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Liver Cancer				
CA150590/P1/ P2/P3/P4 $1,977,778 Open	Schook/ University of Illinois at Urbana-Champaign Solomon; Brown; Boas/ Memorial Sloan Kettering Cancer Center Gaba/ University of Illinois at Chicago	Genetically Inducible Porcine Model of Primary and Metastatic HCC in Comorbidity Host Environments for Interventional Radiology-Guided Detection and Treatment	RP: To develop a porcine model of hepatocellular carcinoma (HCC). Porcine HCC will be characterized in comparison to the human disease to determine the utility of the model system for disease progression, tumor host environmental effects, and disease treatment strategies. MR: HCC is exceedingly common in the US Veteran population due to a high incidence of alcoholic cirrhosis and viral hepatitis.	*New research – no outcomes reported to date*
CA150690 $115,500 Open	Xu/ University of California, Los Angeles	Development of a Synthetic Lethal Drug Combination that Targets the Energy Generation Triangle for Liver Cancer Therapy	RP: To examine the combinatorial effect of inhibiting multiple energy production pathways specific to hepatocellular carcinoma (HCC). By targeting the three main pathways of energy production, the researchers will investigate whether this strategy facilitates tumor clearance unlike single target therapy, which only slows or stops tumor growth without reducing tumor size. MR: Despite the increasing prevalence and lethality of HCC in the United States and among US Veterans, there is a lack of effective and safe drugs available for clinical treatment.	*New research – no outcomes reported to date*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Liver Cancer				
CA150850 $130,500 Open	Liu/ Massachusetts General Hospital	Molecular Characterization of FGFR2 Fusions in Cholangiocarcinoma	RP: To understand the role of fibroblast growth factor receptor 2 (FGFR2) genomic translocations in the pathogenesis of a specific form of bile duct cancer, intrahepatic cholangio-carcinoma (ICC). A new mouse model of ICC will be engineered and small molecule inhibitors of FGFR signaling will be tested for efficacy against patient-derived xenografts. MR: For unknown reasons, diagnoses of ICC, which affects the bile ducts of the liver, are increasing. Patients typically die within 1 year of diagnosis, and treatment with chemotherapy has limited effectiveness. The risk factors for ICC are similar to those of other chronic liver diseases, including chronic alcohol consumption, obesity, and viral hepatitis, all of which affect military personnel and Veterans.	*New research – no outcomes reported to date*
CA150866 $109,480 Open	Tackmann/ University of North Carolina at Chapel Hill	Characterizing the Role of Hep27 in Liver and Colorectal Cancer Stress Tolerance	RP: To investigate the role of Hep27 in conferring resistance to oxidative stress within cancer cells by increasing reactive oxygen species (ROS) tolerance. Using liver and colorectal cancer cell lines, this research will examine the molecular mechanism of ROS tolerance within Hep27-expressing cells and determine if Hep27 expression is a modulator of therapeutic sensitivity. MR: The military population is particularly vulnerable to hepatocellular carcinoma given the higher rates of behavior and environmental exposures that are risk factors of this disease including hepatitis C virus infection, obesity, diabetes, and alcohol abuse.	*New research – no outcomes reported to date*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Liver Cancer				
CA160119 $622,750 Open	Michalopoulos/ University of Pittsburgh	LSP1 Involved in Liver Regeneration Termination, Deleted in 50% of Human Liver Cancer, and Major Determinant of Response to Sorafenib	RP: This project aims to describe the mechanism by which LSP1 negatively interferes with the effectiveness of Sorafenib. Findings from this research would support the use of LSP1 expression in tumors as a novel predictive biomarker of patient response to Sorafenib. A second arm of this project aims to investigate whether drugs that block modification of LSP1 could reinforce the tumor-suppressive effect of unmodified LSP1 in HCC. Work on this project has just initiated. MR: US military personnel have unique exposure related risks associated with the development of hepatocellular carcinoma (HCC). Agent Orange, pesticides, industrial solvents and polychlorinated biphenyl (PCB) are all militarily relevant agents associated with increased risk of HCC.	*Research initiated*
CA160216/P1/P2 $1,613,720 Open	Bardeesy; Zhu/ Massachusetts General Hospital Shokat/ University of California at San Francisco	A Proteomic Co-Clinical Trial of BGJ-398 in FGFR-Driven Biliary Cancers	RP: The goal of this study is to understand the biological consequences of fibroblast growth factor receptor (FGFR) alterations which drive biliary tract cancers. The research team will map the precise biochemical changes that occur as a result of these genetic modifications as well as their impact on pharmacological response. Finally, the team will identify genetic mechanisms which contribute to acquired resistance to FGFR inhibition and develop therapeutic strategies to prevent or overcome resistance. Work on this project has just initiated. MR: More than 1 in 20 cancer patients have a tumor with an FGFR mutation. This includes many cancers with higher incidence within the Veteran population including biliary tract tumors, for which liver cancer is only one example. The increased rates of Hepatitis C infection and liver fluke exposure within this population make biliary tract tumors an important Veterans' health issue.	*Research initiated*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Liver Cancer				
CA160415 $564,365 Open	Averkiou/ University of Washington	Image-Guided, Ultrasound-Mediated Drug Delivery for Hepatocellular Carcinoma Treatment	RP: This project aims to develop an ultrasound-mediated method to enhance chemotherapy delivery to liver cancer. Using both mouse and porcine models they will perform all necessary preclinical testing to evaluate safety and drug delivery efficacy. Work on this project has just initiated. MR: Liver cancer (hepatocellular carcinoma-HCC) is recognized by the VA as a risk factor related to hepatitis C virus (HCV) infection or ionizing radiation exposure during military service.	*Research initiated*
CA160466 $598,070 Open	Simon/ Rockefeller University	Therapy for the Adolescent/Young Adult Cancer Fibrolamellar Hepatocellular Carcinoma	RP: Study of fibrolamellar carcinoma (FLC), a lethal liver cancer, found that a genetic deletion resulting in the fusion of a heat shock protein (DNAJB1) and a protein kinase (PRKACA) is found in 100% of FLC patients. Presence of this fusion protein is sufficient to induce FLC in mouse models. The objective of this study is to identify molecules that block the function of this protein or target it for degradation. Work on this project has just initiated. MR: Fibrolamellar is diagnosed in adolescents and young adults, meaning that active duty military, as well as their children, are in the affected age group.	*Research initiated*
CA160545 $644,754 Open	Welling III/ University of Michigan, Ann Arbor	Therapeutic Targeting of Cancer Stem Cells in Liver Cancer	RP: This project is for the preclinical assessment of two novel hepatocellular carcinoma therapies. Using cholangiocarcinoma and hepatocellular carcinoma (HCC) patient derived xenografts and a mouse model of HCC the PI will assess the impact of these drugs on liver cancer development in vivo. Work on this project has just initiated. MR: Cholangiocarcinoma (CAA) is the second most common primary liver cancer and it arises most frequently during the presence of chronic liver disease, affecting US Veterans at a high rate. Therapies other than surgery for CCA are generally lacking with only one current medical regimen (gemcitabine/ cisplatin) able to extend survival by a mere 3.0 months.	*Research initiated*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Liver Cancer				
CA161009 $237,224 Open	Sarkar/ Stanford University	Role of Tgf Beta and Wnt Signaling in Liver Tissue Homeostasis, Tumorigenesis, and Cancer	RP: This project examines the molecular and cellular regulators of liver proliferation and asks whether disruption of these mechanisms give rise to liver cancer. The PI will engineer mice with specific modifications to pathways important in hepatocyte progenitor cell function and observe the incidence of liver cancer in vivo. Work on this project has just initiated. MR: Broadening our understanding of the genetic, cellular and molecular basis of liver cancer development could lead to the identification of biomarkers for the early detection of liver cancer. This has great potential to impact Service members and their families given that the military population is particularly vulnerable to this cancer.	*Research initiated*
Lymphoma				
CA160361 $554,925 Open	Singh/ Cornell University, Ithaca	Tumor-Specific Lymphoma Organoids for Understanding the MALT1 Pathway for Targeted Drug Therapies	RP: The project aims to engineer a 3D organoid system to understand the role of tumor microenvironment in heterogeneous lymphomas. The PI will determine the integrin-specific ligand and tumor size on the activation of BCR-MALT1- NFkB pathways in ABC-DLBCL2; and determine the sensitivity of ABC-DLBCL to MALT1 inhibitors. MR: Military personal are at greater risk of developing Non-Hodgkin's lymphoma due to the exposure to cytotoxin and chemicals. DLBCL is one of the most aggressive and chemoresistant forms of NHL.	*Research initiated*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Lymphoma				
CA160379 $422,915 Open	Ferrero/ Monash University	Defining the Protective Role of the Innate Immune Molecule, NLRC5, in Stomach B-Cell Lymphomagenesis	RP: Chronic stimulation of immune system by H. pylori may lead to the development of B cell lymphoma in the stomach. This malignancy is known as the mucosa associated lymphoid tissue lymphoma (MALT). The PI identified nucleotide oligomerization domain like receptor caspase activation and recruitment domain-containing 5 (NLRC5) as a potential regulator for the B-cell lymphomagenesis. The study is to understand the mechanism of how NLRC5 regulates B-cell proliferation and survival. MR: H. pylori is a military-relevant risk factor for stomach cancer. This work seeks to define the role of NLRC5 in promoting B cell gastric MALT lymphoma in H. pylori-infected subjects.	*Research initiated*
CA161005 $228,546 Open	Wiewiora/ Cornell University, Weill Medical College	Histone Lysine Methyltransferases-Conformational Dynamics and Selective Inhibitor Design for Chromatin-Modifying Enzymes in Lymphomas and Melanomas	RP: To study the conformational property of histone lysine methyltransferases EZH2 and ETDB1 using molecular dynamics simulations, which could lead to the development of selective inhibitors toEZH2 and SETDB1. MR: Military personnel have greater risk of lymphoma due to deployment-related exposures. This study allows better understanding of the conformational and energetic profiles of EZH2 and SETDB1, which may lead to better design of drugs targeting lymphoma.	*Research initiated*
Melanoma/Skin Cancer				
CA130316 $450,520 Open	Setaluri/ University of Wisconsin–Madison	Noncoding RNA Network in Cutaneous Melanocytes: Regulation by UV and Role in Melanomagenesis	RP: To understand the mechanisms by which UV-induced molecular changes contribute to cutaneous melanoma development to identify tissue biomarkers. PI has identified a UV-regulated miRNA whose presence in melanocytes is significantly reduced upon UV irradiation. Knockdown of this miRNA expression using siRNA increases melanocyte proliferation. MR: Identification of new molecular markers that are regulated by UV will greatly improve the risk assessment of active duty military personnel deployed to sun-intense locations.	*Presentation: 1*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Melanoma/Skin Cancer				
CA130351 $550,800 Open	Wang/ Medical College of Wisconsin	Novel Combinatorial Immunotherapy for Melanoma	RP: To understand the role of V-domain Immunoglobulin Suppressor of T cell Activation (VISTA) in establishing the immunosuppressive tumor microenvironment. Within 2 years of a 3-year award, the PI has mapped the molecular pathway of activity through which VISTA controls inflammatory response. PI has also identified which populations of immune cells are regulated by VISTA, and in the final year of the award PI will examine the effect of VISTA suppression within tumor-bearing mice. MR: Melanoma is recognized as one of the rising cancers developed among military personnel, especially field agents exposed to harsh environmental elements such as sun exposure.	*Presentation: 1*
CA130537 $368,031 Open	Khanna/ University of Connecticut Health Center, Farmington	Development of Cytomegalovirus-Based Vaccines against Melanoma	RP: To develop and test the efficacy of cytomegalovirus (CMV)-based anti-melanoma vaccines expressing single or multiple tumor antigens and to determine the mechanisms of protective immunity provided by these vaccines. Initial studies showed that CMV-expressing tumor antigens can generate potent, long-lasting antitumor immunity due to recruitment of CD8+ and CD4+ T cell recruitment protecting mice from a highly metastatic melanoma. 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 quality of life of the impacted personnel.	*Publications: 2* *Presentations: 3*
CA140020 $489,199 Open	Cui/ Boston University Medical Campus	Dot1L is a Lineage-Specific Tumor Suppressor in Melanocyte	RP: To determine the role of Dot1L in melanoma genesis as well as understanding its function in UV-induced DNA damage and repair. The protective influence of Dot1L on UV-induced melanoma was confirmed in cell lines, patient derived cells as well as in vivo mouse models. The mechanism of this protection currently under investigation. MR: Individuals that serve in tropical areas that receive heavy sun exposure during their early adulthood may be at higher risk of developing melanoma later in life.	*None*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Melanoma/Skin Cancer				
CA140189 $554,400 Open	Fourcade/ University of Pittsburgh	Role of the Inhibitory Receptor TIGIT in the Regulation of CD4+ Tregs in Patients with Advanced Melanoma	RP: This study will assess the role of the inhibitory receptor TIGIT on suppressing the antitumor response of the immune system. Initial results suggest that TIGIT is over expressed in T cell subtypes located in close proximity to the tumor site. The knowledge of this over expression could lead to potential new therapies that target TIGIT for the purpose of alleviating the immunosuppressive environment surrounding solid tumors. MR: UV radiation has been identified as one of the strongest environmental factors for melanoma development. With a significant number of military personnel serving in regions of intense sun exposure, improved therapies will provide higher quality of life for military members and their families.	*Presentations: 3*
CA140203 $552,629 Open	Lund/ Oregon Health & Science University	Melanoma-Associated Lymphangiogenesis, Immune Suppression, and Response to Targeted Therapy	RP: This study aims to better understand the immuno-suppressive cross-talk between the local T-cell environment and the lymphatic vessels in patients and mouse models. Within the first year of the award, the PI has shown that PD-L1, one of the top targets for new antitumor immunotherapies, is modified within the lymphatic vessels at the site of injury. This increase of PD-L1 seems to be due to cytokines produced by CD8+ T-cells. The utility of their findings as potential biomarkers of melanoma survival is currently being investigated. MR: Melanoma incidence in Caucasian active duty military increased rapidly from 1990-1994 to 2000-2004. This increase may be due to significant UV exposure during deployment.	*Publication: 2* *Presentations: 3*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Melanoma/Skin Cancer				
CA140216 $460,477 Open	Harbour/ University of Miami Coral Gable	Development of Targeted Molecular Therapy for Cancers Harboring BAP1 Mutations	RP: Utilize an in vivo high-throughput screen to identify compounds that rescue a developmental phenotype that results from the loss of tumor suppressor gene, BAP1. Promising compounds will also be validated against a mouse model of BAP1-deficient cancers. MR: BAP1 is frequently mutated in the most lethal and treatment-resistant cancers such as melanoma, mesothelioma, and kidney cancer. The development of a BAP1 signaling specific therapeutic is of significant importance to military personnel who are at higher risk of these cancers due to environmental exposures while deployed.	*None to date*
CA140238 $547,200 Open	Su/ University of North Carolina at Chapel Hill	Central Tolerance Blockade to Augment Checkpoint Immunotherapy in Melanoma	RP: Develop an antibody that would enhance the effect of immunological checkpoint inhibitors when used in combination against melanoma growth in mice. In the first 2 years of this award the PI has provided promising evidence that a combination of anti-CTLA4 and anti-RANKL therapy has an additive effect on tumor growth suppression. Two mouse models of melanoma also show prolonged survival with the combination therapy. MR: UV irradiation and other melanoma-predisposing agents are often unavoidable during military deployment. An improvement in immunotherapy for advanced melanoma would broadly benefit military personnel.	*Presentation: 1*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Melanoma/Skin Cancer				
CA140389 $391,766 Open	Siegel/ McGill University	Development of Rational Combination Therapy Strategies for the Treatment of Metastatic Melanoma	RP: Determine whether an antibody-drug conjugate can be employed in combination with current kinase inhibitor therapy to overcome MAPKi drug resistance. In animal models of metastatic melanoma this new combination therapy shows pronounced reduction of tumor volume while individual treatment only slows or suspends tumor growth. Discontinuous use of the combination therapy resulted in enhanced antitumor effect as compared to monotherapy alone. MR: A therapeutic that would dramatically improve both longevity and quality of life for those living with metastatic melanoma would preferentially benefit military personnel who are disproportionally predisposed to melanoma.	*Publications: 1* *Presentations: 3*
CA140415 $283,166 Open	Kimlin/ University of the Sunshine Coast	Is Vitamin D Status at Time of Melanoma Diagnosis Associated with Stage of Tumor?	RP: A correlative study to investigate the association between vitamin D levels and tumor characteristics. PI is actively recruiting patients for this study, MR: Active duty personnel in the US military receive high exposure to solar UV radiation due to their training and deployment in sunny environments, increasing their risk of melanoma.	*None*
CA140485 $474,000 Open	Andarawewa/ University of Virginia	The Therapeutic Effects of Ultrasound-Mediated Immune Responses in Melanoma	RP: A study to determine the utility of a new targeted therapy, focused ultrasound (FUS), in stimulating the immune response to tumors in an animal model of melanoma. The researcher has optimized the FUS parameters and is able to show under different FUS conditions a stimulation or suppression of the immune system. Combinatorial therapy using FUS will be the focus of the next year of funding. MR: The incidence of melanoma is higher in the US military population than in the US population as a whole. Improvement to the current standard of care would therefore affect military families preferentially.	*Presentations: 3* *Funding obtained: 1 grant*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Melanoma/Skin Cancer				
CA140666 $447,000 Open	Xie/ University of Georgia	Treating Melanoma Metastases with a Novel Photodynamic Approach	RP: A project to evaluate the efficacy of a new target therapy to treat metastatic melanoma using X-ray inducible photodynamic therapy. This new treatment method will be characterized in vitro as well as within a mouse model of lung metastasis. The PI has developed the first round of particles for testing, showing promising cytotoxic activity against cell lines. MR: Melanoma incidence rate is roughly 62% greater in active duty military than in the general population. A new treatment for this disease would greatly benefit military personnel and their families.	*Publications: 2* *Presentations: 3*
CA140728 $442,152 Open	Krishna/ Cleveland Clinic Foundation	Polyhydroxy Fullerene Sunscreen for Preventing UV-Induced Skin Cancer	RP: The aim is to engineer a new sustained-release sunscreen formulation using polyhydroxy fullerene, a promising new compound for UV-induced cancer prevention. In the first year of the award in vivo assay development was finalized, drug delivery was optimized, and initial UVB protection was observed. Sustained-release formulations were also developed and their performance in reducing UV-initiated cellular changes will be assessed. MR: The most aggressive form of UV-induced skin cancer is increasing at a higher rate among young military personnel (40%) versus the general public (7%). A new topical sunscreen product to prevent sun exposure would benefit those individuals for whom sun exposure is unavoidable.	*Patent: 1* *Presentations: 3*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Melanoma/Skin Cancer				
CA140744 $489,165 Open	Shah/ Massachusetts General Hospital	Stem Cell-Loaded Oncolytic Viruses for Metastatic Melanomas	RP: Evaluate the therapeutic potential of a virus-mediated tumor-selective therapy in vitro and in a mouse model of melanoma brain metastasis. The PI has shown that virus alone is inefficient at killing melanoma brain metastasis in his mouse model. However, when mesenchymal stem cells (MSC) are infected with the virus and used as a vehicle for transporting these particles to the tumor site, oncogenic cell clearance is greatly increased. MR: Melanoma is of particular interest to the military given that active duty personnel are often required to be outside for prolonged periods of time while stationed in sun-intense locals. Thus, military men and women face the potential for long-term risk of melanoma.	*Publication: 1*
CA150055 $631,899 Open	Kadekaro/ University of Cincinnati	Exploring a New Paradigm in Melanoma Prevention	RP: Determine if there is a correlation between reactive oxygen species and induction of mutagenic DNA lesions within sun exposed skin. Investigate whether antioxidants can prevent this damage. MR: Service members are at a higher risk of developing melanoma due to their occupational exposure to sunlight and other sources of UV radiation. This is particularly true for fair-skinned Service members, who make up 71% of the total enlisted military personnel. The expanded knowledge of melanoma initiation gained from this study could lead to improved interventions that protect our Service members and the general public from developing melanoma.	*New research – no outcomes reported to date*
CA150068 $558,000 Open	Moon/ University of Michigan	A New Vaccination Strategy for Treatment of Melanoma	RP: A study to develop new technology that will induce potent immune responses against primary and metastatic melanoma using melanoma cell lysate-loaded nanoparticles. MR: Melanoma is of particular interest to the US military because military personnel are often exposed to hazardous physical, chemical, and/or biological factors for extended periods including documented chronic exposure to UV radiation, electromagnetic fields, jet fuel, and volatile organic materials.	*New research – no outcomes reported to date*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Melanoma/Skin Cancer				
CA150197 $674,932 Open	Zheng/ Massachusetts General Hospital	Role of the Lipid Phosphatase INPP48 in the Development of Resistance to BRAF Pathway Inhibition	RP: Characterize the signaling mechanism underlying the tumor suppressor effects of INPP4B, a lipid modifying protein, in melanoma and elucidate its contribution to the development of resistance to BRAF pathway inhibition. MR: Military Service men and women who work in sun-intense areas have great risk for developing melanoma. In fact, it has been demonstrated that the incidence of melanoma is higher in the military population than in the general US population.	*New research – no outcomes reported to date*
CA150256 $620,000 Open	White/ Cornell University Ithaca	Defining the Role of Stem Cell Activation in Initiating Melanoma and Melanocytic Tumor Recurrence	RP: Determine if melanocyte stem cell (MCSC) activation by UV light exposure can act as a primary initiator of tumor growth in melanoma-prone skin. The PI has demonstrated that MCSC quiescence prevents melanoma tumor formation whereas MCSC activation facilitates rapid onset of tumor growth. Additionally, MCSCs within the skin exposed to UVB demonstrated induction of ectopic pigmentation and macroscopic tumor formation within 14 days of exposure. MCSCs protected from UVB remained in quiescence and did not initiate tumors. MR: Military members recently deployed to Iraq and Afghanistan report excessive levels of sunlight exposure, causing concern for their heightened risk for melanoma.	*None*
CA150340 $665,999 Open	Yan/ Yale University	Dissecting the Roles of ARID2 Tumor Suppressor in Metastatic Melanoma	RP: Determine how putative tumor suppressor ARID2, an epigenetic regulator, controls melanocyte reprogramming, and investigate whether targeting another epigenetic regulator RBP2 can be used to treat patients with ARID2 loss. MR: As the risk of melanoma is highly elevated by heavy sunlight exposure for Service members dispatched to areas like Iraq and Afghanistan, these studies will significantly benefit these Service members and their families.	*New research – no outcomes reported to date*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Melanoma/Skin Cancer				
CA150356 $611,214 Open	Gilmour/ Lankenau Institute for Medical Research (LIMR)	Targeting Increased Polyamine Transport of Resistant Melanomas	RP: Investigate the utility of the polyamine transport system as a therapeutic target for drug-resistant melanoma tumor cells.. MR: A recent study of active duty military personnel aged 18 to 56 (who served between 2000 and 2007) found that their melanoma risk was higher than the general population. Thus, military personnel across multiple branches of the military will also clearly benefit from new medical intervention.	*New research – no outcomes reported to date*
CA150391 $606,236 Open	Wang/ University of North Carolina at Chapel Hill	Tissue-Engineered Cancer Metastasis to Improve the Abscopal Effect and Cancer Immunotherapy in Melanoma	RP: Use patient-derived cancer cells to induce immunological clearance of tumors. Will engineer 3D melanoma lung metastases from animals and humans and evaluate their utility as immunizing agents. 3D cultures will be lethally irradiated and injected back in to cancer-containing host to determine if these cells can stimulate an anti-cancer immune response. MR: Improvements in management of metastatic melanoma can be particularly beneficial to military populations. Melanoma is more common in members of the military than in the general population. Also, compared to other solid tumor malignancies, metastatic melanoma frequently affects patients in their third and fourth decades of life during which time many are still active duty members of the Armed Services.	*New research – no outcomes reported to date*
CA150437 $610,200 Open	Moubarak/ New York University School of Medicine	Functional Role of Epigenetic Regulation in Melanoma Brain Metastasis	RP: Characterize the proteins involved in PHF8 and CHD7-mediated metastasis and determine the utility of these proteins as clinical biomarkers of melanoma. In the first year of the award the PI has confirmed that both PHF8 and CHD7 removal impaired melanoma cell invasion in vivo and in vitro. In the following years, the PI will further investigate the mechanism of these proteins in promoting melanoma metastasis. MR: Military personnel are exposed to UV-induced melanoma burden. Since 50% of metastatic melanomas ultimately lead to brain metastasis, gaining understanding of mechanisms of metastasis and conception of novel therapies is crucial for advances in patient care for Service members, their families, and other military beneficiaries.	*None*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Melanoma/Skin Cancer				
CA150492 $632,000 Open	Zaidi/ Temple University	UV-Induced Epigenetic Field Effect as a Target for Melanoma Therapy and Prevention	RP: Investigate the role of UV irradiation-induced epigenetic changes in melanoma initiation and determine the utility of these changes as biomarkers. In the first year of the award the PI has generated all mouse models for the in vivo and in vitro work associated with this project and will investigate the UV-induced changes in melanocytes in the remaining performance time. MR: UV radiation from the sun is the most ubiquitous environmental carcinogen, and military personnel are especially prone to high-level exposure to UV radiation during deployments to global areas with high intensities of UV radiation. These occupational exposures increase their susceptibility to melanoma manifold. Understanding the mechanisms and identifying the biomarkers of melanoma susceptibility, initiation, and progression is vital to devising preventive and therapeutic strategies for military personnel as well as the general public.	*Presentations: 2*
CA150523 $528,815 Open	Thomas/ Georgia Tech Research Corporation	Targeted Immunotherapy for Melanoma	RP: Evaluate whether lymph node drug targeting can improve melanoma immunotherapy by leveraging a nanoparticle technology that significantly improves lymph node delivery of currently approved immunotherapy drugs. MR: Melanoma disproportionately affects US military personnel, suggesting a role for military Service-related exposure to carcinogens.	*New research – no outcomes reported to date*
CA150619/P1/P2 $2,132,675 Open	Herlyn/ Wistar Institute Cooper; Wargo/ University of Texas MD Anderson Cancer Center	Understanding the Immune Biology of Checkpoint Inhibitors to Develop New Strategies for Therapy	RP: Evaluate the efficacy of the combination of two recently approved immune checkpoint inhibitors, Nivolumab and Ipilimumab, in patients with advanced melanoma. Work is accompanying an ongoing clinical trial at the MD Anderson Cancer Center. MR: Eighty-five percent of all melanomas are induced by excessive sun exposure, which for the last 15 years many members of the military had to confront. Starting in the near future, the incidence of melanoma (and other skin cancers) is expected to drastically increase in active duty members and Veterans.	*New research – no outcomes reported to date*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Melanoma/Skin Cancer				
CA150630/P1/P2 $2,197,999 Open	Weber/ New York University School of Medicine Gabrilovich; Hu/ Wistar Institute	Myeloid-Derived Suppressor Cells in Checkpoint Protein Inhibition for Melanoma	RP: Evaluate the immunoregulatory activity of DS-8273a, an antibody therapeutic that activates TRAIL-DR5, when administered in combination with nivolumab in subjects with unresectable Stage III or Stage IV melanoma, and explore the mechanisms by which the TRAIL-DR5 agonistic antibody depletes myeloid derived suppressor cells (MDSC). MR: Active military are at increasing risk of melanoma due to high levels of sunlight exposure, the most significant risk factor for melanoma in most areas of the world in which the US military is currently engaged.	*New research – no outcomes reported to date*
CA150776 $131,250 Open	Badrinath/ Dana-Farber Cancer Institute	Development of Epitope-Focused Tumor Vaccine to Prevent Escape from Immune Surveillance by the NKG2D Pathway	RP: Optimize a bacteria-based vaccine and evaluate whether it provides protection against subcutaneous melanomas and metastasis in mice. MR: Active duty Service members are often exposed for prolonged periods to UV radiation, which is the major risk factor for the development of malignant melanoma.	*New research – no outcomes reported to date*
CA150796 $124,874 Open	Zhang/ Yale University	Epigenetic Regulation of Histone Demethylase JARID1B in Melanoma	RP: Investigate the mechanism by which JARID1B regulates melanoma stem cells, and provide evidence for whether JARID1B targeting should be based on its demethylase activity or on its interactions with key transcription factors or co-activators such as PGC-1α. MR: Military Service members and Veterans face higher risk for melanoma and other skin cancers.	*New research – no outcomes reported to date*
CA150804 $127,125 Open	Ribeiro Muniz/ Icahn School of Medicine at Mount Sinai	Endogenous Alarmins in the Progression of Melanoma	RP: To identify the receptors involved in metalloproteinase 2 (MMP-2) signaling and investigate the mechanisms by which MMP-2 promotes melanoma progression. Inhibitors of MMP-2 will also be developed. MR: It has been reported that melanoma rates are higher in active duty military personnel when compared to the general population and that exposure to sunlight and UV rays can induce skin cancer later on in life.	*New research – no outcomes reported to date*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Melanoma/Skin Cancer				
CA150818 $115,500 Open	Hong/ University of California Los Angeles	Melanoma Drug Addiction and Its Therapeutic Implications	RP: A study to characterize a newly described phenomenon in cancer treatment, termed "drug-addiction," where melanoma tumor cells become dependent on BRAF and MEK inhibitors after chronic treatment with these common chemotherapeutics. MR: Studies have shown melanoma to be the second most common cancer in the military, with incidence rapidly rising due to constant exposure to sunlight and inadequate protection.	*New research – no outcomes reported to date*
CA150852 $80,934 Open	Barkauskas/ Queensland Institute of Medical Research	The Role of Adenosine A2BR in Metastatic Melanoma	RP: Determine the role of adenosine 2B receptor (A2BR) in melanoma metastasis by studying A2BR expression on the tumor cell surface and/or endothelium. Assess the use of tumor-infiltrating immune cell activators in combination with A2BR inhibitors as metastasis preventative therapy. MR: Studies have found that 77% of military personnel report being exposed to bright sunlight for more than 4 hours a day while working, potentially exposing them to high doses of intermittent UV light, which has been shown in preclinical models to drive melanoma metastasis.	*New research – no outcomes reported to date*
CA150863 $101,290 Open	Chang/ Memorial Sloan Kettering Cancer Center	A Therapeutic TCR Mimic Monoclonal Antibody for Intracellular PRAME Protein in Melanomas	RP: Investigate the mechanism by which immunological presentation of a peptide specific to melanoma cells (PRAME(300-309)) is initiated. Determine if utilizing this peptide as a marker for melanoma cells is a viable strategy for new immunotherapies. MR: Because incidence of melanoma is higher in active duty Service members, the knowledge gained from these studies will help design future immunotherapies for military personnel.	*Publication: 1*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Melanoma/Skin Cancer				
CA150887 $112,125 Open	Daenthanasanmak/ Medical University of South Carolina	Tumor-Specific Th1/Th17 Hybrid Immunotherapy against Established Melanoma	RP: Characterize a novel cell type, hybrid Th1+/Th17+ T cells, regarding the molecular mechanisms of cell survival in vivo, immunological memory phenotype, stem cell-like phenotype, and cytotoxic function in tumor eradication. MR: Melanoma is one of the deadliest forms of skin cancer, particularly in the late stages when the malignant cells have metastasized into other vital organs such as lung, brain, and abdominal organs, and affects the general population and military personnel alike.	*New research – no outcomes reported to date*
CA150892 $146,250 Open	Li/ Sanford-Burnham Medical Research Institute, La Jolla	Control of Immune Checkpoints by the Ubiquitin Ligase RNF5: Implications for Melanoma	RP: To test whether ubiquitin ligase RNF5 regulates the fidelity of a signaling pathway that regulates immune cell checkpoints. This work will identify novel targets for future melanoma treatment based on controlling RNF5 activity. MR: Melanoma often develops following prolonged sun exposure. Accordingly, exposure of our Service members to sun during deployment puts young men and women at risk for developing melanoma. For those potentially affected, the disease would likely manifest itself after they leave the Service and would impact not only their health but also the emotional and financial well-being of their families.	*New research – no outcomes reported to date*
CA150903 $118,500 Open	Wilson/ University of Virginia	Ligand Expression on Tumor-Associated Vasculature Orchestrates CD8+ T-Cell Infiltration into Tumors	RP: A study to define the association between homing receptor (HR) ligand expression within the tumor vasculature and the presence of tumor-infiltrating lymphocytes (TIL) using human melanoma samples. Methods to modify HR expression will also be investigated. MR: Melanoma commonly occurs in young adults; many active duty Service members are young adults who are frequently overexposed to harmful UV sunlight. This puts them at a high risk for getting melanoma and/or other skin-associated cancers.	*New research – no outcomes reported to date*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Melanoma/Skin Cancer				
CA160105 $554,400 Open	Kulkarni/ University of California at Los Angeles	Evaluating Heterogeneity and Response to Treatment in Melanoma Using Circulating Tumor Cells	RP: This project aims to isolate and characterize circulating tumor cells from melanoma patients. The PI will collect blood samples from melanoma patients undergoing treatment to identify molecular predictors of sensitivity/resistance to immunotherapies based on profiles of the circulating tumor cells found in their blood. Work on this project has just initiated. MR: Melanoma is increasing in incidence among Service members and Veterans. Earlier detection of disease and earlier detection of recurrence after treatment will be critical for reducing the morbidity and mortality of this disease.	*Research initiated*
CA160224 $510,231 Open	Wallace/ Kansas State University	Cutaneous Human Papillomaviruses as Cofactors in Nonmelanoma Skin Cancer	RP: This project will investigate the mechanism by which transient HPV infection drives increased risk for melanoma and other skin cancers. The PI will characterize the effect of HPV infection on DNA repair pathways and genome fidelity checkpoint signaling within cell line models of human skin cancer. Work on this project has just initiated. MR: Extensive attempts to minimize the risk posed by ultraviolet light and ionizing radiation have failed to mitigate the elevated risk for skin cancers faced by our military Service members. This project will investigate other factors that may be contributing to the high prevalence of these malignancies.	*Research initiated*
CA160347 $694,500 Open	Lian/ Brigham and Women's Hospital	Epigenetic Reprogramming and Skin Cancer Prevention	RP: A project to investigate the role of epigenetic mechanisms in UV-induced skin carcinogenesis. The PI will characterize the epigenetic changes in UV-damaged melanocytes and keratinocytes and determine whether modifying the epigenetic landscape to pre-UV treatment status is sufficient to prevent squamous cell carcinoma (SCC) in vivo. Work on this project has just initiated. MR: Melanoma and SCC are of particular interest to the DoD due to occupational exposure to UV radiation and higher incidence of skin cancers of military personnel.	*Research initiated*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Melanoma/Skin Cancer				
CA160385 $681,572 Open	Tsao/ Massachusetts General Hospital	Elucidating Clonal Competition Through Fluorescent Color Coding of Melanoma Cells	RP: The project will investigate how a clonal population of cells becomes the dominant components of solid tumors. Using a newly developed fluorescent tool to track cell lineage, the PI will investigate the molecular basis of clonal expansion within tumors and determine the intra-cellular and extra-cellular factors supporting this type of growth. Work on this project has just initiated. MR: Melanoma and other skin cancers are by far the most common cancer group among military personnel. Skin cancer treatment in the VA system has been estimated to exceed $100 million per year not accounting for metastatic disease developing from melanomas.	*Research initiated*
CA160489 $576,000 Open	Rai/ The University of Texas MD Anderson Cancer Center	Epigenetic Effectors of Tumor Response to Immune Checkpoint Inhibitors	RP: A project to determine if DNA modification states associate with immune checkpoint inhibitor response in melanoma. The PI will monitor epigenetic marker changes from tumor and blood samples collected from patients treated with FDA-approved immunotherapies and determine if these markers correlate with clinical outcome. Additionally, the PI will determine if functional modification of proteins responsible for DNA modification can increase the antitumor effect of anti-PD1 therapy in vivo. Work on this project has just initiated. MR: Military personnel have increased risk for melanoma because active duty personnel are often required to be outside for prolonged periods and may be exposed to potential risk factors such as UV rays in the sunlight.	*Research initiated*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Melanoma/Skin Cancer				
CA160521 $545,486 Open	Singh/ The University of Texas MD Anderson Cancer Center	B-Cell Mediated Antimelanoma Immunity	RP: The PI will investigate the role of B cells in enhancing the anti-melanoma activity of CD8+ T cells. This project will utilize tissue samples collected from patients treated with different immunotherapies to determine whether and how B cell phenotypes correlate with clinical outcomes. Work on this project has just initiated. MR: Melanoma is one of the most frequently diagnosed cancers among VA cancer patients, making it a serious healthcare burden.	*Research initiated*
CA160657 $670,000 Open	Lu/ Yale University	The Impact of Somatic Hematopoietic Mutations on Melanoma Tumorigenesis	RP: Examine whether loss of TET2, a protein involved in DNA methylation and gene regulation, within hematopoietic stem cells, will significantly alter melanoma tumorigenesis in vivo using mouse models. The PI will characterize cellular and molecular changes induced by TET2 loss in these models. Work on this project has just initiated. MR: Health risks of military activities such as ionizing radiation, carcinogens, and UV will lead to genetic mutations in cells of various tissues. The project will examine whether mutations in tissue other than skin can regulate melanoma tumorigenesis.	*Research initiated*
CA160858 $543,335 Open	Cui/ University of New Mexico, Albuquerque	Development of Diagnostic Tools for Metastatic Melanoma via Imaging of Heparanase Activity	RP: Aims to develop new imaging tools to monitor tumor growth and metastasis. The PI will use newly developed probes to monitor heparanase activity in melanoma cells. High heperanase activity has been linked with increased tumor metastasis and poor post-surgery survival. If successful, this project could lead to new imaging approaches for detection of metastatic disease. Work on this project just initiated. MR: Malignant melanoma is one of the most common cancers among active duty Service members, with ~2,000 Service members (mostly Caucasians) diagnosed between 2000 and 2011. Service members are usually discharged with melanoma if it has metastasized and they are limited in the performance of their duties.	*Research initiated*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Melanoma/Skin Cancer				
CA160896 $646,313 Open	Cantor/ Dana-Farber Cancer Institute	Immunotherapy of Melanoma: Targeting Helios in the Tumor Microenvironment for Effector Cell Conversion	RP: Focuses on a specific transcription factor, Helios, believed to play a critical role maintaining Treg activity. The PI will investigate whether modifying Helios signaling could promote the conversion of suppressor cells to effector cells, which have the capability of killing tumors. Work on this project has just initiated. MR: Military personnel may be more vulnerable to melanoma due to deployment in regions of the world, e.g., Afghanistan, Iraq, where exposure to excessive levels of UV radiation from sunlight is unavoidable.	*Research initiated*
CA160997 $235,500 Open	Bajpai/ Stanford University	Investigating Epigenomic Reprogramming in Human Melanoma Development	RP: Goal is to develop an epigenomic and transcriptomic map of melanocyte differentiation stages. Will help increase understanding of extent to which presence of common tumor-associated gene mutations drive melanocyte epigenomes towards melanomagenesis. Work on this project has just initiated. MR: Military personnel and Veterans belong to high-risk category with increased likelihood of developing melanoma in their lifetimes compared to the general population. Mapping the pathways that drive melanomagenesis could identify novel therapeutic targets for the treatment of this disease.	*Research initiated*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Mesothelioma				
CA130197 $391,875 Open	Shukla/ University of Vermont	Exosomes in Development and Therapy of Malignant Mesothelioma	RP: To study the role of exosomes, small lipid bound signaling packages, in the development and therapy of malignant mesothelioma to determine whether exosomes secreted from asbestos-exposed human lung macrophages and epithelial cells can transform human mesothelial cells. Initial research indicates that exosomes generated from epithelial cells exposed to asbestos contain a unique proteomic signature which may be responsible for their uptake by mesothelial cells. MR: Military and Veteran populations are at a higher risk of developing mesothelioma due to Service-related exposures to asbestos. Because of the long latency period of development of this cancer, cases will continue to appear in Veteran and military populations for decades to come.	*Publication: 1* *Presentations: 2*
CA140269 $400,613 Open	Najmunnisa/ University of Florida	Epha2 -/- NK Cell Therapy Against Malignant Pleural Mesothelioma	RP: This study aims to characterize the mechanism of tumor growth inhibition by natural killer (NK) cells lacking the EphA2 gene using a model of malignant pleural mesothelioma. The PI has confirmed that NK cells lacking EphA2 expression are more cytotoxic than wildtype cells. Targeting these NK cells to MPM cells show a significant reduction on tumor growth in co-culture systems. The in vivo activity of these MPM targeting NK cells will be tested in the second year of the project. MR: Thirty percent of new cases of malignant pleural mesothelioma are reported in Veterans each year. Due to environment exposures including asbestos, Veterans are at a high risk of developing this fatal disease.	*Presentations: 1*
CA140385 $633,056 Open	Zauderer/ Memorial Sloan Kettering Cancer Center	BAP1 Mutations in Malignant Pleural Mesothelioma: Biology, Clinical Phenotypes, Radiotherapy Response, and Target Discovery for Somatic and Germline Mutations	RP: A study to understand the prevalence and association between mutations in the tumor suppressor gene BAP1 and clinical outcomes of mesothelioma. The PI has obtained biopsies from more than 100 individuals and is in the process of analyzing the prevalence of somatic and germline mutations within these patient samples. MR: Malignant mesothelioma disproportionately affects active duty Service members and Veterans due to their exposure to asbestos in the military.	*None*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Mesothelioma				
CA150220 $616,000 Open	Yang/ University of Hawaii	Identification and Validation of Novel Germline DNA Variants Associated to Increased Risk of Malignant Mesothelioma	RP: To identify novel genes whose mutations predispose individuals to malignant mesothelioma. Whole exome sequencing of malignant mesothelioma patients with a genetic history of cancer will be used to identify susceptibility variants and the functional effect of identified mutations will be assessed in asbestos-exposed cell lines and mice. MR: The majority of US Veterans were exposed to asbestos at some point during their military service in shipyards, aircrafts, etc. Indeed, malignant mesothelioma is disproportionally overrepresented in the military as Veterans account for nearly one-third of all malignant mesothelioma diagnoses.	*New research – no outcomes reported to date*
CA150300 $553,945 Open	Bertino/ University of Hawaii	Preclinical Development of TVAX: An Advanced Multiantigen Vaccine for Therapy and Prevention of Malignant Mesothelioma	RP: To determine the therapeutic efficacy of a multi-epitope immunization platform termed mTvax. Using a mouse model of malignant mesothelioma, T-cell activation, tumor burden, and survival will be assessed in vaccinated mice. Development and evaluation of a human specific Tvax is also proposed. MR: More than 300 products, e.g., valves, brakes, gaskets, cements, adhesives, and pipe coverings, containing asbestos, were used by the military, primarily by the Navy, making Navy Veterans one of the most at-risk groups for developing asbestos-related malignant mesothelioma. In fact, it is estimated that one malignant mesothelioma patient out of every four is a former Navy man or shipyard worker.	*New research – no outcomes reported to date*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Mesothelioma				
CA150671/P1/ P2/P3/P4 $1,902,900 Open	Yang; Carbone/ University of Hawaii Pass/ New York University School of Medicine Kanodia/ Cedars-Sinai Medical Center Mak/ University Health Network, Toronto	HMGB1 and Its Isoforms as Biomarkers for Mineral Fiber Exposure and MM Detection	RP: To define the role of HMGB1, a regulator of inflammatory response, within malignant mesothelioma (MM) development and progression. Aims to develop new animal models of malignant mesothelioma to assess whether HMGB1 expression is critical for malignant mesothelioma following asbestos exposure and whether disruption of HMGB1 signaling is a viable intervention target. The project will also assess the utility of HMGB1 isoforms as biomarkers of mineral fiber exposure. MR: More than 300 products, e.g., valves, brakes, gaskets, cements, adhesives, and pipe coverings, containing asbestos, were used by the military, primarily by the Navy, making Navy Veterans one of the most at-risk groups for developing asbestos related malignant mesothelioma. In fact, it is estimated that one malignant mesothelioma patient out of every four is a former Navy man or shipyard worker. Naval Veterans who served from the WWII era to the Vietnam War hold the greatest risk of asbestos-induced MM as all sailors and shipyard workers were exposed via navigation rooms, mess halls, and sleeping quarters where asbestos was used.	*New research – no outcomes reported to date*
CA150787 $74,980 Open	Chee/ University of Western Australia	Characterizing Neo-Antigen T Cell Responses in Mesothelioma Immunity	RP: A study to determine the utility of antigenic markers of malignant mesothelioma (MM) as targets for cancer immunotherapies. The work aims to examine the immunomodulatory effect that mesothelioma-specific antigens have after cancer treatment and to assess whether vaccination against these antigens can sensitize malignant mesothelioma mice to treatment. MR: Active members of the military have increased risk over the general population of being exposed to asbestos in shipyards, aircrafts, and other military occupations. In the US, Veterans of the military account for nearly one-third of all MM diagnoses.	*New research – no outcomes reported to date*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Mesothelioma				
CA160250 $613,417 Open	Heasley/ University of Colorado Denver	Identifying TME-Derived Pathways for Cotargeting with FGFR1 in Mesothelioma	RP: This project will examine the molecular changes that occur between mesothelioma cells and the tumor microenvironment (TME) as a result of FGFR-specific TKI treatment. By examining the FGFR TKI-induced changes that occur within the TME of tumor-bearing mice, the researcher hopes to identify key mediators of TKI resistance and on-treatment tumor progression. Work on this project has just initiated. MR: Evidence demonstrates that former members of the military, especially US Navy Veterans, are among those most affected by asbestos exposure. Overall, experts estimate that approximately 30 percent of all cases of mesothelioma are diagnosed in Veterans.	*Research initiated*
CA160891/P1 $1,491,517 Open	Harpole/ Duke University Bueno/ Brigham and Women's Hospital	Military Exposure-Related Pleural Mesothelioma: An Innovative Translational Approach to Inform Novel Molecular-Targeted Treatment Development	RP: Using a civilian and military population, the research team aims to redefine the classification of malignant pleural mesothelioma into biologically and prognostically distinct subgroups. From this work they hope to develop treatment plans rationally designed around the specific diagnostic/prognostic biomarkers unique to the newly defined subtypes. Work on this project has just initiated. MR: This project will utilize samples collected from an asbestos-exposed cohort of military Veterans to validate newly identified biomarker signatures of malignant pleural mesothelioma.	*Research initiated*
Myeloproliferative Disorders				
CA140408 $462,000 Open	Wilson/ University of New Mexico Health Sciences Center	Calreticulin and Jak2 as Chaperones for MPL: Insights Into MPN Pathogenesis	RP: Test the hypothesis that JAK2, MPL, or CALR mutation leads to abnormal signaling and eventually leads to essential thrombocythemia or primary myelofibrosis. MR: Military members are at higher risk for myeloproliferative neoplasms (MPN). The understanding of pathogenesis, diagnosis, and treatment of MPNs will benefit military members.	*New research – no outcomes reported to date*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Myeloproliferative Disorders				
CA150085 $565,162 Open	Felices/ University of Minnesota Twin Cities	Enhancing Natural Killer Cell Mediated Targeting and Responses to Myeloid Leukemias	RP: The study aims to enhance the immunotherapeutic value of NK cells against myeloid leukemia. The approach is to create TriKEs that target NK cells to myeloid tumor cells. MR: Exposure to ionizing radiation, chemicals, and other agents during deployment increases the incidence of myeloid malignancies. Novel therapeutic reagents that target myeloid malignancies are needed to help the Warfighters to combat these diseases.	*Research initiated*
CA150493 $556,200 Open	Fleischman/ University of California Irvine	Inflammation as a Driver of Clonal Evolution in Myeloproliferative Neoplasm	RP: To understand the mechanism that causes excessive tumor necrosis factor alpha (TNFα) production in myeloproliferative neoplasm (MPN), and to identify agents to reduce TNFα production. MR: Many Veterans with MPN had radiation or chemical exposures during their military service.	*Research initiated*
CA150529 $696,000 Open	Fraenkel/ Beth Israel Deaconess Medical Center, Boston	Discovering New Drug Targets in Radiation-Induced Myeloproliferative Neoplasms	RP: To perform the first systematic evaluation of genetic alterations in patients with MPN who have previously been exposed to ionizing radiation. MR: Service members have increased exposure to ionizing radiation, which causes damages to the bone marrow. This study will lead to new drug targets to radiation-induced MPNs.	*Research initiated*
CA150767 $125,909 Open	Ghaffari/ Icahn School of Medicine at Mount Sinai	Dual Inhibition of FLT3 and RET Pathways by ON150030 as Novel Strategy for AML Therapy	RP: To test the therapeutic value of a new therapeutic agent, ON150030 for acute myelocytic leukemia (AML). MR: This novel agent could be used as an alternative therapy to Service members with AML who do not respond to the current treatment regimen.	*Research initiated*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Neuroblastoma				
CA130153 $630,000 Open	Freeman/ St. Jude Children's Research Hospital	The Development of a Primary Neural Crest Assay for Neuroblastoma Oncogenesis	RP: To rapidly screen for neuroblastoma (NBL)-causing genes and to understand how specific target gene gains and losses collaborate during tumorigenesis. Results so far indicate that the loss of the tumor suppressor genes Arid1a and Chd5 are both necessary for tumor formation. The PI is now using the model system to determine which oncogenes are gained during tumorigenesis. MR: The health and welfare of the force are partially determined by the health/welfare of their supportive families. Military missions benefit when Warfighters' families are healthy and well.	*Presentations: 3*
CA130396 $521,460 Open	Stewart/ St. Jude Children's Research Hospital	Tumor Growth Model with PK Input for Neuroblastoma Drug Development	RP: To develop a comprehensive computational tumor model using pharmacokinetic (PK) and pharmacodynamic measurements to predict drug response patterns in neuroblastoma (NB) tumors. The PI constructed the proposed physiologically-based PK (PBPK) model using two neuroblastoma therapeutics and is testing the model's predictive capabilities. MR: The health and welfare of the force are partially determined by the health/welfare of their supportive families. Military missions benefit when Warfighters' families are healthy and well.	*Presentations: 4*
CA140035 $570,600 Open	Gustafson/ University of California, San Francisco	Drugging the AXIN/GSK/MYCN Complex through an Allosteric Transition in Aurora Kinase A in Neuroblastoma and Medulloblastoma	RP: To test the hypothesis that the scaffold protein AXIN is a member of AURKA/MYC complex observed in MYC/MYCN tumors. PI found that an AURKA conformation disruptor does not disrupt the interactions between MYC, AURKA, and Axin. He also developed novel methods for measuring the components and activity of the MYC/AURKA/Axin complex. MR: MYC, MYCN, AURKA, and AXIN are prominent drivers of oncogenesis in a wide array of adult and pediatric tumors, including medulloblastoma and neuroblastoma. Novel therapeutics targeting these molecules will benefit children of military families and active Service members/Veterans.	*None to date*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Neuroblastoma				
CA140114 $402,430 Open	Bollard/ Children's Research Institute at CNMC	Utilizing TGF-beta Resistant Natural Killer Cells for Adoptive Transfer to Overcome Tumor Immune Evasion	RP: PI demonstrated that umbilical cord blood natural killer (NK) cells expand to a greater degree than peripheral blood NK cells and that she can successfully transduce these cells with the dominant negative TGF-beta receptor. Following transduction these cells maintain their specificity. PI has also successfully established xenogeneic murine models for testing the efficacy of the cellular products in vivo. MR: Several studies have concluded that the incidence of solid tumors is higher among children of Vietnam War Veterans than in the general population. If successful, this project could make cord blood-derived TGF-β-resistant NK cells available as an "off-the-shelf" product to high-risk patients with neuroblastoma.	*Publications: 2*
CA140291 $495,000 Open	Takahashi/ University of Southern California	Peptidic Inhibitors of N-myc for Treatment of Neuroblastoma	RP: Design drug-like peptides that bind to N-myc and test their efficacy in treating neuroblastoma. PI has identified several peptides that look encouraging based on bioinformatics analyses and is currently testing the most promising peptides. MR: Service members who have children affected by neuroblastoma would undoubtedly benefit the most from the potential treatment options that arise from this proposal.	*None to date*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Neuroblastoma				
CA150634/P1/P2 $1,733,196 Open	George; Gray/ Dana-Farber Cancer Institute Gustafson/ University of California, San Francisco	Therapeutic Strategies for MYCN-Amplified Neuroblastoma	RP: The short-term goal is to develop novel therapeutic options for patients with high-risk neuroblastoma based on disrupting the oncogenic functions of deregulated MYCN, either at the mRNA and/or the protein level. The PIs will develop and test the clinical applicability of these first-in-class tool compounds to inhibit MYCN transcription and hasten degradation of the MYCN protein respectively both singly and in combination with currently utilized agents. The long-term goal is to produce durable responses in patients with MYCN-amplified neuroblastoma, both at initial diagnosis and at relapse. MR: Neuroblastoma accounts for nearly 15% of all deaths due to childhood cancer. Although the diagnosis and treatment of neuroblastoma exact a heavy emotional and financial toll on all families, the impact is likely to be greater in military families, who often have one or more members on active duty. The stresses imposed by prolonged hospital admissions for intensive treatment or its complications and the need to travel far from home to seek specialized care and experimental treatments following relapse cannot be overemphasized.	*New research – no outcomes reported to date*
CA150773 $122,979 Open	Qadeer/ Icahn School of Medicine at Mount Sinai	Investigating the Mechanisms Underlying ATRX Mutant Neuroblastoma	RP: To test the hypothesis that ATRX mutations culminate in epigenetic and transcriptional alterations in neuroblastoma by (1) mapping ATRX binding sites in wild-type neuroblastoma and compare them to ATRX mutant protein localization; and (2) investigating genes that are deregulated in ATRX mutant neuroblastome that may be contributing to increased migration and invasion. MR: As military members and their families are strongly affected when their children are diagnosed with this disease, it is imperative to identify novel therapeutic targets to improve clinical outcomes and alleviate this additional emotional and physical stress. By interrogating the unexplored epigenetic mechanisms that contribute to aggressive neuroblastoma, the PI aims to develop rational therapies to better manage the burden of disease.	*New research – no outcomes reported to date*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Neuroblastoma				
CA150807 $114,000 Open	Xu/ University of North Carolina at Chapel Hill	Exploiting Hypoxia for T-Cell Immunotherapy in Neuroblastoma	RP: Hypoxia is commonly associated with neuroblastoma and inhibits the function of naïve and central-memory T cells. However, effector memory T cells, commonly utilized in immunotherapies, show enhanced proliferation in hypoxia. The PI proposes that the proliferation differences are attributed to differential expression of hypoxia inducible factor 1-α (HIF1-α), and proposes to define the mechanisms of this differential expression. PI will also explore how this mechanism might be exploited to improve immunotherapy activity. MR: This project could lead to better and safer treatment options for neuroblastoma and ultimately will alleviate the physical and mental burden for active duty Service members and their children who suffer from neuroblastoma.	*New research – no outcomes reported to date*
CA160360 $556,500 Open	Zhu/ Mayo Clinic and Foundation, Rochester	Understanding the Cooperation Between LMO1 and MYCN in Neuroblastoma Metastasis Using a Novel Zebrafish Model	RP: The PI will use a validated zebrafish model of neuroblastoma metastasis, combined with state-of-the-art live imaging, tumor cell transplantation, CRISPR-cas9-mediated genome editing, and a novel tissue-specific, conditional doxycycline-regulated system, to identify key pathways downstream of the oncogene, LMO1, that interact with a second oncogene, MYCN, in neuroblastoma metastasis. MR: Neuroblastoma is the most common extracranial solid tumor of childhood, accounting for about 10% of all cancer-related deaths in children. The development of neuroblastoma in children of military families carries the added risk of disrupted service time due to the family's involvement in the child's care, especially during emergency episodes.	*Research initiated*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Pancreatic Cancer				
CA130288 $415,200 Open	Wolpin/ Dana-Farber Cancer Institute	Comprehensive Evaluation of Altered Systemic Metabolism and Pancreatic Cancer Risk	RP: To identify and understand, via a prospective plasma metabolite profiling study, the metabolic changes that signal the presence of early pancreatic tumors and promote their growth. The PI identified over 4,000 plasma metabolites from 1,500 pancreatic cancer patient and control samples; over 1,000 were deemed of sufficient quality for further analyses. The PI is currently building models that incorporate these metabolites with known pancreatic risk factors with the goal of stratifying a population's disease risk. MR: Pancreatic cancer is one of the most lethal forms of cancer affecting Service members, Veterans, and military beneficiaries and their families.	*Publication: 4* *Presentations: 27*
CA140228 $531,685 Open	Cukierman/ Institute for Cancer Research	Pancreatic Cancers Desmoplasia: The Possible Bridge Impending Nerve Infiltration and Neoplastic Escape	RP: Determine if the neural synapse maintenance protein, G1, promotes and stabilizes neuronal recruitment to pancreatic tumors and promotes metastasis. Using a novel multichannel immunofluorescence technique to study different types of cells present in pancreatic tumors, the PI found neuronal proteins that are upregulated in tumor-associated fibroblasts but not normal fibroblasts. Furthermore, the PI found that tumor-associated fibroblasts and neuronal cells interact with each other through neuronal synaptic stabilizer proteins, and lack of these proteins reduces neuronal cell growth. MR: Risk factors for pancreatic cancer, such as diabetes, poor diet, smoking, etc., are overrepresented in both active duty military personnel and Veterans. This study will help close some of the gaps in diagnosis and treatment of military and Veteran personnel.	*Publications: 2* *Funding Obtained: 1 (F32 training grant)*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Pancreatic Cancer				
CA140634 $479,488 Open	Stanger/ University of Pennsylvania	A Cell-Based Approach to Early Pancreatic Cancer Detection	RP: Determine if pancreatic cells circulating in the blood can be used as biomarkers for detecting pancreatic cancer. To date, the PI has obtained proof-of-concept that a magnetic nanopore chip can be used to provide a rapid and significant enrichment of tumor cells from a murine blood sample, and the enriched cells can be used in downstream molecular analysis. MR: There is currently no test to diagnose pancreatic cancer at a stage early enough to effect interventions most likely to work. The creation of such a detection tool would greatly benefit military personnel.	*None to date*
CA140731 $403,459 Open	Der/ University of North Carolina at Chapel Hill	Targeting K-RAS for Pancreatic Cancer Treatment	RP: To fully define KRAS dependency of pancreatic tumors and identify the specific pathways that drive K-RAS dependency. The PI has characterized numerous pancreatic cancer cell lines and identified a panel of kinases that are most often mutated in pancreatic cancer. Current studies are investigating if any of these kinases may be druggable targets. MR: Pancreatic cancer is currently the fourth major cause of cancer deaths for US active Service members and their families, with only a 6% 5-year survival rate.	*Presentations: 4*
CA140792 $575,997 Open	Curran/ University of Texas MD Anderson Cancer Center	Immunologic Rejection of Pancreatic Cancer without Autoimmune Side Effects	RP: Test the hypothesis that a combination of three antibodies (αCTLA-4, αPD-1, and α4-1BB) can successfully activate an immune response against pancreatic cancer. The PI found that, in a mouse model of pancreatic cancer, therapy combining anti-CTLA-4/PD-1 antibodies with immune stimulatory molecules extended mouse survival and reduced toxicity. Current work is investigating the mechanisms of these observations. MR: Pancreatic cancer is one of the most lethal forms of cancer affecting Service members, Veterans, and military beneficiaries and their families.	*Presentations: 2*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Pancreatic Cancer				
CA150378 $575,938 Open	Dougan/ Dana-Farber Cancer Institute	Directly Conjugated Single-Domain VHHs Targeting MHC Class II Prime T-Cell Responses against Pancreatic Cancer Neoantigens	RP: To date, immunotherapies have largely failed in treating pancreatic cancer patients. The PI plans to implement a novel mechanism to active CD4 T cells outside of the pancreas, in the lymph nodes and spleen, and then have those T cells infiltrate the pancreatic tumor and cause tumor rejection. MR: Exposure to pesticides such as DDT that were used in Vietnam has been correlated with increased risk of pancreatic cancer. Ionizing radiation and exposure to chemical carcinogens are direct causes of cancer due to their ability to damage DNA, and the mutational load of these cancers tends to be high. Mutational load and, correspondingly, the number of potential neoantigens that can be targeted by the immune system are correlated with the success rate of immunotherapy.	*New research – no outcomes reported to date*
CA150550 $685,600 Open	Iacobuzio-Donahue/ Memorial Sloan Kettering Cancer Center	Somatic Mosaicism for Cancer Predisposition Genes and Pancreatic Cancer	RP: The objective of this proposal is to determine the prevalence of somatic mosaicism for cancer predisposition genes in normal tissues from patients with pancreatic cancer. MR: In the military population, environmental exposures such as Agent Orange have been linked to an increased incidence of a variety of malignancies and known cancer syndromes that may affect the ability of an individual to effectively serve. Somatic mosaicism may provide an alternative and more probable explanation for cancers occurring in young men and women currently serving or having served in the military as opposed to a presumed link to a military occupational exposure.	*New research – no outcomes reported to date*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Pancreatic Cancer				
CA150626/P1/ P2/P3/P4 $1,717,906 Open	Maitra; Neelapu; Yee; Overman/ University of Texas MD Anderson Cancer Center Mettu/ Duke University	Preclinical and Human Correlative Studies of a Novel Bruton Tyrosine Kinase Inhibitor in Pancreatic Cancer	RP: This team science award is testing the hypothesis that a Bruton's tyrosine kinase inhibitor (BTKI) will enhance the efficacy of immune checkpoint blockade therapies. In novel preclinical mouse models, the group will test the influence of the BTKI on immune cell subsets and the efficacy of novel immunotherapy regimens combined with the BTKI. MR: The PIs expect that their proposal will enable them to develop a novel combination regimen for active or Veteran Armed Forces personnel with pancreatic ductal adenocarcinoma, which will enable a meaningful improvement in survival rather than a statistical improvement.	*New research – no outcomes reported to date*
CA150842 $128,250 Open	Patra/ Massachusetts General Hospital	Decoding Metabolic Programs Underlying Pancreatic Cancer Progression	RP: To study the metabolic alterations in pancreatic cancer cells with mutant GNAS and compare them to pancreatic cancer cells with other defined genetics. In particular, to study how mutations in the GNAS gene deregulate mitochondrial and lipid metabolism and then study how GNAS-regulated pathways drive alternative metabolic programs. MR: Pancreatic cancer is one of the most lethal forms of cancer affecting Service members, Veterans, and military beneficiaries and their families. This study could identify new therapeutic targets.	*New research – no outcomes reported to date*
CA160097 $702,000 Open	Commisso/ Sanford-Burnham Medical Research Institute, La Jolla	NHE7 as a Novel Drug Target in Pancreatic Cancer	RP: The PI will test the hypothesis that the suppression of the sodium/hydrogen ion exchanger, NHE7, diminishes pancreatic tumor growth and that its unique localization to the plasma membrane of tumor cells can be harnessed to develop novel therapies. MR: Accumulating evidence from numerous studies indicates that military service is a risk factor for pancreatic cancer. This proposed research could lead to the development of new treatment paradigms within the Military Health System in the near future.	*Research initiated*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Pancreatic Cancer				
CA160269 $588,346 Open	Lynch/ Institute for Cancer Research	Towards Precision Prevention: Testing a Novel Risk Prediction Algorithm in Pancreatic Cancer	RP: The PI plans on comprehensively evaluating the effect of genetic, molecular, and individual level risk factors on pancreatic cancer outcomes using machine learning models in a nested case-control study of 350 pancreatic cancer cases and 1400 controls in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO). The goal is to identify high-risk subgroups with combined risk factor profiles (i.e., biology and behavior) and potentially translate this information into multi-modal, precision-based prevention, screening, or treatment recommendations. MR: Pancreatic cancer is a major cause of death among US Veterans. Women who served in Vietnam are more likely to die of pancreatic cancer than civilians. Further, military personnel have a high prevalence of risk factors implicated in pancreatic cancer, particularly high rates of obesity, alcohol consumption, and cigarette smoking among men.	*Research initiated*
CA160311 $552,600 Open	Dudeja/ University of Miami	Effect of HSP70 in Immune Environment on Pancreatic Cancer Growth	RP: The PI will evaluate the hypothesis that HSP70 in the immune environment supports pancreatic cancer growth and that deletion of HSP70 in immune cells leads to inhibition of tumor growth through T cell-mediated cancer cell killing. MR: These studies have significant military relevance as the US Veteran population, by virtue of increased excessive use of tobacco and alcohol, is more prone to pancreatic cancer.	*Research initiated*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Pancreatic Cancer				
CA160339 $637,743 Open	Mostoslavsky/ Massachusetts General Hospital	SIRT6 Suppresses Pancreatic Cancer via the Oncofetal Protein Lin28b	RP: The PI aims to define the biological and molecular mechanisms by which the SIRT6/LIN28B axis drives the proliferation of pancreatic ductal adenocarcinoma (PDAC) cells; also, determine the downstream consequences of Lin28b activation in this subset of pancreatic cancers, and define the molecular mechanisms behind the increased metastatic potential of Sirt6(low)/Lin28(high) PDACs. MR: Military personnel appear to represent a particularly vulnerable population with increased incidence of this disease. The PI will collaborate with the VA Boston Healthcare System to assess whether military personnel specifically carry the unique genetic signature of Sirt6(low)/Lin28(high).	*Research initiated*
CA160771 $617,542 Open	Yu/ Emory University	Improving Pancreatic Cancer Therapy Through Understanding and Exploiting SAMHD1 in DNA Repair	RP: The objective is to determine whether SAMHD1 can be utilized as a biomarker to discriminate treatment resistance in pancreatic cancer. MR: Military members are at increased risk for pancreatic cancer due to exposure to genotoxic agents such as ionizing radiation (IR) and environmental carcinogens. Improved treatment approaches would have a particularly profound impact on military members because pancreatic cancer is disproportionally represented in the military.	*Research initiated*
CA160954 $239,850 Open	Banerjee/ University of Illinois at Chicago	Structural and Biochemical Differences Between the Most Common Pancreatic and Colorectal Cancer G12D and G12V Mutants of K-RAS	RP: The PI will conduct a structural study to identify a GTP-independent activation mechanism in a mutant form of K-RAS commonly observed in pancreatic cancer. MR: Currently, there are no K-RAS inhibitors on the market. Understanding the mechanisms of K-RAS activation by oncogenic mutations and interactions with Ca2+-CaM may lead to development of novel anti-cancer therapeutics.	*Research initiated*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Pancreatic Cancer				
CA161010 $232,500 Open	Purohit/ University of Michigan, Ann Arbor	Role of ATDC in the Regulation of Antioxidant Response in Pancreatic Cancer	RP: The PI proposes testing the hypothesis that ATDC is a key regulator of NRF2-mediated antioxidant response and cellular metabolism in pancreatic ductal adenocarcinoma (PDA). MR: Completion of these studies will greatly improve our understanding of PDA biology and uncover novel therapeutic targets beneficial to everyone, including Service members, Veterans, and their families.	*Research initiated*
Pediatric Brain Tumor				
CA130273 $522,410 Open	Yun/ Jackson Laboratory	Cell of Origin and Cancer Stem Cell Phenotype in Medulloblastomas	RP: Test the hypothesis that the cellular context in which an initiating oncogenic event occurs may have a dominant role over the specific oncogene function in determining the molecular phenotype of a tumor. The PI has been developing an appropriate mouse model to test this hypothesis. MR: Health and welfare of the force are partially determined by the health and welfare of their supportive families. Military missions benefit when the Warfighters' families are healthy and well.	*None to date*
CA130319 $331,063 Open	Ying/ Hugo W. Moser Research Institute at Kennedy Krieger, Inc.	Modeling Aggressive Medulloblastoma Using Human-Induced Pluripotent Stem Cells	RP: Determined that neural progenitors can be induced from human-induced pluripotent stem cells and form MYC-driven Group 3 medulloblastomas, which can subsequently be cultured. This model system was used to show that inducing expression of the transcription factor Atoh1leads to tumor formation. MR: The health and welfare of the force are partially determined by the health and welfare of their supportive families. Military missions benefit when the Warfighters' families are healthy and well.	*Presentations: 2*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Pediatric Brain Tumor				
CA130436 $421,077 Open	Hinchcliffe/ University of Minnesota, Twin Cities	Defects in Histone H3.3 Phosphorylation and ATRX Recruitment to Misaligned Chromosomes during Mitosis Contribute to the Development of Pediatric Glioblastomas	RP: Showed that p53 cell cycle arrest triggered by chromosome missegregation is mediated via a novel signaling mechanism dependent upon phosphorylation at a specific histone site and ATRX recruitment to lagging (missegregating) chromosomes. This system serves as a type of proximity sensor, and its dysregulation may lead to tumorigenesis. MR: The health and welfare of the force are partially determined by the health and welfare of their supportive families. Military missions benefit when Warfighters' families are healthy and well.	*Publications: 2* *Presentations: 11*
CA140056 $459,463 Open	Castellino/ Emory University	Mechanisms of PPM1D in Growth and Treatment Responsiveness of Pediatric DIPGs	RP: Results show that mutation of PPM1D accelerates the growth of murine and human, patient-derived DIPG cells. Furthermore, treatment with a small molecule PPM1D inhibitor suppresses the growth of DIPG cells and enhances the efficacy of IR by promoting cell death. MR: This study could lead to novel therapeutics to treat children diagnosed with DIPG, thus decreasing the impact of cancer on Service members.	*Presentation: 1* *Funding Obtained: 1(NGO)*
CA140089 $529,200 Open	Friedman/ University of Alabama at Birmingham	Intraventricular Delivery of Engineered Oncolytic Herpes Simplex Virotherapy to Treat Localized and Metastatic Pediatric Brain Tumors	RP: There is a significant need to develop more effective and less neurotoxic treatments for pediatric brain tumors. The PI determined that toxicity to current oncolytic virus therapy is due to the live virus itself, as inactivated virus did not induce a toxic response in mice. Additional studies showed that a lower dose of virus did not result in a toxic response, and the lower dose was able to prolong survival of mice with medulloblastoma tumors and reduce spinal metastases in treated mice. MR: This proposed project seeks to expand treatment options by improving the delivery and development of a novel, targeted therapy, which may improve outcomes and reduce toxicity in children with brain tumors, thereby benefitting active duty Service members and their families.	*None to date*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Pediatric Brain Tumor				
CA160264 $590,400 Open	Huang/ Hospital for Sick Children	Defining the Role of and Mechanism by Which the Chloride Channel CLIC1 Regulates Brain Tumor Growth	RP: The PI will test the hypothesis that the chloride channel CLIC1 is a medulloblastoma (MB)-specific regulator and potential therapeutic target. He will define the role of CLIC1 in a mouse model of MB, determine how it regulates MB tumor growth, and investigate the therapeutic potential of targeting CLIC1 and potassium channels. MR: Any diagnosis of a pediatric brain tumor, including MB, is devastating to a military family. It also reduces the ability of the Service member to fulfill their duties thus decreasing the readiness of our Military.	*Research initiated*
CA160373 $677,999 Open	Law/ Cornell University, Weill Medical College	Multifunctional Nanofiber for Convection-Enhanced Delivery of Theranostics to Diffuse Intrinsic Pontine Glioma	RP: The PI and his collaborators will formulate a peptide nanofiber (NFP) to carry a drug cocktail (panobinostat and GSK-J4) directly to DIPG tumors via convection-enhanced delivery (CED). The team will then test the pharmacokinetics and efficacy of the system in preclinical DIPG mouse models. MR: Childhood cancer disproportionately disrupts our military families. Actively serving military families already suffer from long-distance relationships. A DIPG diagnosis of a child puts the entire family into a stressful, desperate, and helpless position	*Research initiated*
CA160414 $549,000 Open	Sayour/ University of Florida	RNA-Nanoparticles Targeting H3.3 K27M Epitopes in Diffuse Intrinsic Pontine Glioma	RP: The PI will test in preclinical models of DIPG the hypothesis that lysosomal associated membrane proteins (LAMP) conjugated with RNA nanoparticles (RNA-NPs) targeting neoantigens will enhance MHC II presentation and potentiate anti-DIPG activity. MR: The ability to select therapeutic strategies that are more likely to be effective against individual tumors without toxicity, as proposed in this application, will have a dramatic impact on civilians and military personnel and their families.	*Research initiated*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Pediatric Brain Tumor				
CA160525/P1/P2 $1,343,263 Open	Alonso/ University of Navarra Gomez-Manzano; Fueyo/ The University of Texas MD Anderson Cancer Center	Oncolytic Immunotherapy for Diffuse Intrinsic Pontine Gliomas	RP: PIs propose to develop improved tumor-targeted oncolytic adenoviruses to treat diffuse intrinsic pontine gliomas. They will first assess the activation, proliferation, and development of memory cell tumor infiltrates in tumor samples collected from a complete adult glioma clinical trial. They will then perform preclinical studies in immunocompetent models of DIPG to develop improved viruses, with the aim goal of improving immune cell response in DIPG. MR: To date DIPG is an incurable disease that adversely affects the preparedness of our military.	*Research initiated*
CA160704 $559,800 Open	Venkataraman/ University of Colorado at Denver	Dependency of H3K27M-Mutated DIPG on BMI1-Mediated Cell Self-Renewal	RP: The PI proposes investigating the role of BMI1 in enhancing DIPG tumor growth and hopes to identify the molecular consequence of H3K27 mutation with BMI1 in triggering cancer stem cell proliferation. Upon successful completion of this work, he will investigate the effect of a small molecule inhibitor of BMI1 in DIPG cell radio-sensitization and evaluate the effectiveness of BMI1 inhibition as a specific therapeutic for treating these infiltrating tumors. MR: Improving the care of pediatric patients will allow Service members to return quickly to military service as the time needed for intensive care of their dependents will be lowered, enabling them to balance the needs of their families with the needs of their service position.	*Research initiated*
Stomach Cancer				
CA160916 $262,500 Open	Panditharatna/ Children's Research Institute	Preclinical Precision Targeting of Major Driver Mutations in Childhood Diffuse Intrinsic Pontine Glioma	RP: The PI will use preclinical models to test five FDA-approved therapeutics and determine their ability to target H3.K27M and TP53 mutations, which are commonly observed in diffuse intrinsic pontine glioma (DIPG). MR: DIPG is a deadly pediatric brain tumor that affects about 200-300 families every year in the United States, including numerous military families.	*Research initiated*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Stomach Cancer				
CA150079 $639,556 Open	Bass/ Dana-Farber Cancer Institute	Developing Mouse Models of Stomach Cancer with CRISPR/Cas9 Technologies and Environmental Exposures	RP: To develop mouse model for stomach cancer using CRISP/Cas9 technology MR: Service members are exposed to infectious and chemical agents that increase the risk for stomach cancer. This study seeks to develop technologies that lead to better understanding and treatment for stomach cancer.	*Research initiated*
CA150132 $576,000 Open	Gough/ Monash University	Defining the Efficacy of Blocking Serine Phosphorylated STAT3 in the Treatment of Gastric Cancer	RP: To test the hypothesis that targeting mitochondrial pS727 STAT3 will suppress inflammation associated tumorigenesis. MR: Service members have a higher rate of *Helicobacter pylori* infection than civilians. Chronic *H. pylori* infection is a major risk factor for stomach cancer. This study will lead to new therapeutic options for stomach cancer and benefit the military community.	*Research initiated*
CA150252 $575,954 Open	Akbani/ University of Texas MD Anderson Cancer Center	Analysis of Gastric Adenocarcinoma Data in a Pan-GI Context to Reveal Genes, Pathways, and Interactions that Yield Novel Therapeutic Advantages	RP: This study aims to identify genes, pathways for gastric cancer by analyzing Pan-GI data. MR: Service members have increased risk for stomach cancer when deployed to regions with higher rate of *H. pylori* infection. This study will expand our knowledge of gastric cancer and could potentially improve treatment options for the military.	*Research initiated*
CA150334 $640,000 Open	Ajani/ University of Texas MD Anderson Cancer Center	Exploiting RhoA Mutations in Diffuse Gastric Adenocarcinoma and Targeting Intertwined RhoA and Yap1 Pathways for Therapeutic Advantage	RP: To test the hypothesis that RhoA and Yap1 pathways are novel targets for diffuse gastric adenocarcinoma (dGAC) and the dual inhibition will provide added advantage against dGAC. MR: Service members have increased risk for stomach cancer when deployed to regions with higher rate of *Helicobacter pylori* infection. This study could lead to new treatment options for stomach cancer.	*Research initiated*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Stomach Cancer				
CA150357 $388,380 Open	Bao/ Brigham and Women's Hospital	Plasma Metabolomic Fingerprint of Early Gastric Cancer	RP: A study to describe the metabolomics fingerprint associated with gastric cancer. PI will measure the individual metabolite levels from patients' plasma samples to determine gastric cancer risk. From these data, a definition of the metabolic pathways important in development and maintenance of gastric cancer will be generated. MR: Gastric cancer is a Service-connected malignancy for Service members who experienced hazardous exposure to ionizing radiation. In addition, research has shown that US Soldiers living under field conditions are at great risk of *H. pylori* infection, which is the main cause of gastric cancer.	*Research initiated*
CA150375 $607,557 Open	Reyes/ University of Texas Medical Branch Galveston	Molecular Characterization of *H. pylori* Strains and Biomarkers in Gastric Cancer	RP: This study aims to understand the genetic features of *Helicobacter pylori* strains linked to stomach cancer; and to identify biomarkers for stomach cancer. MR: Service members deployed to regions with higher *H. pylori* prevalence are at risk for *H. pylori* infection and stomach cancer. Stomach cancer is one of the top cancers treated in VA system.	*Research initiated*
CA150646/P1/P2 $2,081,946 Open	Janjigian; Lewis/ Memorial Sloan Kettering Cancer Center Tavazoie/ Rockefeller University	89Zr-Trastuzumab-PET, Rapid Autopsies, and Patient-Derived Xenografts to Determine the Extent of Clonal Evolution in Treatment-Refractory HER2+ Gastric Cancer	RP: This study aims to understand the mechanism of drug resistance in esophagogastric cancer (EG). The hypothesis is that HER2 levels between primary tumor and metastasis sites may contribute to the drug resistance. Furthermore, mutation of key kinases and deregulated expression of small non-coding RNAs (miRNAs) contribute to drug resistance in HER2-positive EG. MR: EG cancer is rapidly increasing and has high impact on the military and Veteran populations.	*Research initiated*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Stomach Cancer				
CA150647/P1/ P2/P3/P4 $1,931,391 Open	Korn; Collisson; Fong; Ashworth/ University of California, San Francisco Janjigian/ Memorial Sloan Kettering Cancer Center	Targeting BRCAness in Gastric Cancer	RP: To test a combination therapy using immunotherapy and PARP inhibition to treat gastric cancers displaying BRCAness. MR: Service members are exposed to higher risks of *Helicobacter pylori* infection and radiation exposure resulting in increased risk of gastric cancer.	*Research initiated*
CA150742 $89,700 Open	Sung/ National Cancer Institute	Discovery and Validation of Plasma DNA Methylation Biomarker for Detection of Stomach Cancer	RP: To identify and validate plasma DNA methylation as a potential biomarker for the detection of stomach cancer. Will use blood samples from patients and case-control subjects to identify and test biomarker utility. MR: If shown to be valid, these biomarkers, which are based on a simple blood test, have the potential to transform stomach cancer screening and reduce disease-related mortality in the general public as well as in military members, Veterans, and their families.	*Research initiated*
CA150895 $131,250 Open	Zhang/ Dana-Farber Cancer Institute	The Function of RHOA Mutations in the Development of Diffuse Gastric Cancer	RP: To test the hypothesis that genomic perturbation of the RHO pathway complements the effect of CDH1 (cadherin-1) inactivation to promote the formation of diffusive gastric cancer. MR: Service members are exposed to higher risks of *Helicobacter pylori* infection and radiation exposure, resulting in increased risk of gastric cancer.	*Research initiated*
CA160399 $568,800 Open	Choi/ Vanderbilt University Medical Center	Gastric Carcinogenesis in a Novel Genetically Engineered Mouse Model	RP: To test the hypothesis that activated K-RAS in metaplastic lineages derived from mature chief cells will lead to development of gastric adenocarcinoma. MR: Service members are at higher risk for stomach cancer due to the increased exposure to *Helicobacter pylori.* This study may lead to the development of new therapeutics to stomach cancer.	*Research initiated*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Stomach Cancer				
CA160431 $558,001 Open	El Zaatari/ University of Michigan, Ann Arbor	Targeting B Cell-Mediated Type II Autoimmunity in Gastric Carcinogenesis	RP: *Helicobacter pylori* causes gastric metaplasia, which predisposes to gastric carcinogenesis (GC). The aim of this study is to establish autoimmunity as a causative mechanism in metaplasia. The hypothesis is B cell-mediated type 2 autoimmunity contributes to the natural progression of metaplasia. MR: *H. pylori* is a major risk factor for gastric cancer. Military personnel are at higher risk of acquiring *H. pylori* and therefore at higher risk for GC. This study could provide a better understanding of mechanism of how *H. pylori* may lead to GC.	*Research initiated*
CA160433 $611,722 Open	Song/ The University of Texas MD Anderson Cancer Center	Immune-Suppression and Tumor-Stromal Interaction Mediated by Galectin-3 in Gastric Cancer - Implications of Novel Therapeutic Strategies	RP: To test the hypothesis that Gal-3 induces immune suppression by upregulating immune checkpoint protein PDL1 and CD47 in tumor cells, and activation of TAF to secrete inflammatory cytokines (CSF1/CCR2) in the stroma. MR: Japan, Korea, and Taiwan have higher rates of gastric cancer. The major risk factors are *Helicobacter pylori*, food pickled with carcinogens, and high salt diet. Troops deployed to these regions are at higher risk for GC. This study aims to improve survival of GC patients in our troops and their families.	*Research initiated*
CA160445/P1/P2 $1,577,193 Open	Ajani; Hanash; Calin/ The University of Texas MD Anderson Cancer Center	Discover Novel Therapeutic Strategies for Peritoneal Metastases from Gastric Adenocarcinoma	RP: To conduct molecular profiling of cancer stem cell pathways in peritoneal carcinomatosis (PC) and to identify molecular targets in human PC cells through a multi-omics platform. MR: Service members are at higher risk for gastric cancers. Identification of novel drug targets will benefit Service members with gastric cancers.	*Research initiated*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Stomach Cancer				
CA160479 $531,636 Open	Goldenring/ Vanderbilt University Medical Center	Identification of Metaplastic and Pre-Neoplastic Stem/Progenitor Cells	RP: Gastric cancer arises from precancerous metaplastic lineages. This project aims to understand the earliest stages of GC to find therapies that can prevent or reverse pre-cancerous lesions. MR: Service members are at higher risk for GC. This study will provide insights into the early processes of GC that could be targets for early therapeutic intervention to reverse pre-cancerous lesions and prevent gastric cancer development.	*Research initiated*
CA160616 $633,483 Open	Lee/ The University of Texas MD Anderson Cancer Center	Marker-Based Targeting of Chemoresistant Subtype of Gastric Cancer Discovered by Proteomics	RP: The study is to (1) develop and validate biomarkers for subtype A in clinical samples; (2) validate resistance in PDX model, (3) determine the molecular mechanisms of chemoresistance in subtype A. MR: Gastric cancer is considered a Service-connected malignancy due to exposure to hazardous to ionizing radiation to *Helicobacter pylori*. This study hopes to develop biomarker-based treatment strategy for GC patients.	*Research initiated*
CA160688 $518,400 Open	Wang/ University of California, San Francisco	Cytoskeletal Modulation Results in Drug Resistance of Gastric Cancer Through Inhibition of p53-Mediated Apoptosis	RP: Inhibition of the cytoskeletal RhoA-ROCK-myosin axis results in attenuation of p53, decreased apoptosis, and increased tumor survival. This study is to test whether MYH9 can be a biomarker for treatment response and also studies if re-activated p53 can enhance tumor killing. MR: Gastric cancer is considered a Service-connected malignancy due to exposure to hazardous to ionizing radiation to *Helicobacter pylori*. This study hopes to develop new biomarker and treatment strategy.	*Research initiated*
CA160801 $619,375 Open	Korn/ University of California, San Francisco	Rational Therapies for Diffuse-Type Gastric Cancer	RP: To test the hypothesis that TGF-beta and related pathways may be therapeutic targets in diffuse type gastric cancer. MR: Military personnel are at higher risk for gastric cancer due to the exposure to *Helicobacter pylori* infection and radiation exposure. This study will help to develop more efficacious treatments for this disease.	*Research initiated*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Stomach Cancer				
CA160928 $239,999 Open	Veeranki/ The University of Texas MD Anderson Cancer Center	Cyclin-Dependent Kinase 9, a Potential Therapeutic Target in Gastric Adenocarcinoma: An In Vitro and In Vivo Efficacy Study	RP: To test the hypothesis that CDK9 is a critical mediator of growth and metastatic progression in GAC. Functional downregulation of CDK9 will inhibit local growth and distant metastasis in GAC. MR: Military personnel are at higher risk for gastric cancer due to exposure to *Helicobacter pylori* infection and radiation exposure. This study will help to develop new inhibitors of CDK9 to treat GAC.	*Research initiated*
CA160948 $262,500 Open	Nagaraja/ Dana-Farber Cancer Institute	Cyclin E1 in Gastric Cancer	RP: To test the hypothesis that cyclin E1 (CCNE1) activation promotes genomic instability and the development of GC. MR: Military personnel are at higher risk for gastric cancer. This study will provide a better understanding of the pathogenesis of GC by developing mouse models of this disease.	*Research initiated*

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APPENDIX A: FISCAL YEAR 2009 (FY09)-FY15 RESEARCH PROGRESS AND MILITARY RELEVANCE OF CLOSED AWARDS

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Blood Cancer				
CA100164 $545,036 Closed	Trobridge/ 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 MDS and AML transplanted mice for biomarker screening. Identified a candidate gene that is differentially expressed in AML patients. 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).	*Publications: 5* *Presentations: 2* *Patent: 1 provisional patent*
CA100254 $440,220 Closed	Sarantopoulos/ University of North Carolina at Chapel Hill	BAFF-Driven Targeted Immunotherapy for Patients with Leukemia	RP: Study on how BAFF (B-cell activating factor) promotes specific anti-leukemia responses to develop novel therapeutic agents for leukemia. Established two murine leukemia models. Identified B-cell subsets related to chronic graft versus host disease and graft versus leukemia. MR: The environmental exposure to cytotoxins and chemicals during deployment is associated with higher incidence of leukemia.	*Presentations: 1* *Funding obtained: 1*
CA100623/P1 $1,073,580.38 Closed	Lanza; Tomasson/ Washington University	Treatment of Multiple Myeloma with VLA4-Targeted Nanoparticles Delivering Novel c-MYC Inhibitor Prodrug	RP: Develop nanoparticle encapsulated prodrug to inhibit Myc and test its efficacy on multiple myeloma (MM). The Myc prodrug markedly improved bioactivity in several myeloma cell types. The prodrug extended the days of survival of mice with metastatic myeloma by 50%. MR: Male Veterans using VA hospitals are at 51% increased risk of MM compared to the general public.	*Publications: 2* *Presentations: 44* *Funding obtained: 1*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Blood Cancer				
CA110020 $242,777.96 Closed	Masamha/ University of Texas Health Science Center at Houston	Deciphering the Mechanism of Alternative Cleavage and Polyadenylation in Mantle Cell Lymphoma (MCL)	RP: Study the mechanism of cyclin D1 mRNA alternative cleavage and polyadenylation in Mantle Cell Lymphoma. Identified CFIm25 as a global regulator of polyadenylation for over 1,400 genes including cyclin D1. CFIm25 depletion corresponds with enhanced tumorigenicity. MR: The environmental exposure to cytotoxins and chemicals during deployment is associated with a higher incidence of blood cancers.	*Publications: 2 (1 in Nature)* *Presentations: 4*
CA110081 $369,468.69 Closed	Newman/ Stanford University	Genomic Signatures for Integrative Models of Clinical Heterogeneity in Patients with Follicular Lymphoma	RP: Development of a novel method to determine follicular lymphoma patients' responsivity to treatment. Developed a novel computational method to validate therapeutic response. MR: The environmental exposure to cytotoxins and chemicals during deployment is associated with a higher incidence of blood cancers.	*Publications: 3* *Presentations: 3* *Funding obtained: 2* *Software: 1*
CA110096 $218,526.12 Closed	McClellan/ 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 to determine f potential triggers for disease regression. MR: The environmental exposure to cytotoxins and chemicals during deployment is associated with a higher incidence of blood cancers.	*Publications: 1* *Presentations: 1*
CA110584 $262,647.71 Closed	Reuther/ H. Lee Moffitt Cancer Center & Research Institute	Enhancing Targeted Therapy for Myeloproliferative Neoplasms	RP: Focuses on the molecular targeted therapy for myeloproliferative neoplasms and how it can be enhanced by combination therapy with modulators of lipid biosynthesis. MR: The environmental exposure to cytotoxins and chemicals during deployment is associated with a higher incidence of blood cancers.	*Degrees obtained: 1 Ph.D. awarded* *Employment: 1 (Student received Postdoctoral Fellowship)*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
CA110791 $310,965.72 Closed	Wei/ University of Texas MD Anderson Cancer Center	Innate Immunity Dysregulation in Myelodysplastic Syndromes	RP: Demonstrated that TLR2 innate immune signaling is excessively activated in MDS bone marrow stem/progenitor cells. Led to a Phase I/II clinical trial to assess the antibody OPN-35 in MDS patients. 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.	*Publications: 5* *Presentations: 7*
Blood Cancer				
CA110834 $200,000 Pending Closeout	FitzGerald/ 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. Cloned, sequenced, and engineered the variable region of two surface immunoglobulin molecules. MR: The environmental exposure to cytotoxins and chemicals during deployment is associated with a higher incidence of blood cancers.	*Patent: 1 provisional patent*
CA120025 $415,470 Closed	Reagan/ Dana-Farber Cancer Institute	Reciprocal Interactions between Multiple Myeloma Cells and Osteoprogenitor Cells Affect Bone Formation and Tumor Growth	RP: Developed a bone cancer model that supports long-term culture and imaging of myeloma cells, high-throughput drug screening, vessel formation, and osteogenesis in the presence of cancer. MR: MM is a disease of particular relevance to our military Veterans. Male Veterans using VA hospitals are at 51% increased risk of MM compared to the general public.	*Publications: 7* *Presentations: 14* *Funding obtained: 2* *Employment: 1* (Assistant Professorship)
CA120064 $308,400 Pending Closeout	Brander/ Duke University	Understanding Drug Resistance to Targeted Therapeutics in Malignant B-Cell Lymphoproliferative Disorders	RP: Seeks to determine mechanisms for drug resistance in chronic lymphocytic leukemia 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.	*Presentations: 16* *Funding obtained: 2*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
CA120120 $344,007 Closed	Xie/ Rutgers, State University of New Jersey	Regulation of Mitochondria Function by TRAF3 in B Lymphocytes and B-Cell Malignancies	RP: Study the role of mitochondria in TRAF3, novel tumor suppressor, in induced apoptosis in B cells. MR: This study seeks to find new avenues for the prevention and treatment of major blood cancers, which impact many military personnel.	*Publications: 4* *Presentations: 20*
CA120128 $399,600 Pending Closeout	Halene/ 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 myelodysplastic syndrome (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.	*Presentations: 3*
Blood Cancer				
CA120184 $397,693 Closed	Lin/ Dana-Farber Cancer Institute	Understanding Selective Downregulation of c-Myc Expression through Inhibition of General Transcription Regulators in MM	RP: Demonstrated selective downregulation of c-Myc expression through inhibition of general transcription regulators in MM. MR: MM is a disease of particular relevance to military Veterans. Male Veterans using VA hospitals are at 51% increased risk of MM compared to the general public.	*Publications: 7* *Presentations: 2* *Software: 1 database, 1 software tool* *Employment: 1 (PI obtained a faculty position)*
CA120373 $374,400 Closed	Liu/ Indiana University, Indianapolis	Modulating Leukemia-Initiating Cell Quiescence to Improve Leukemia Treatment	RP: Determined the role of Necdin in the initiation of AML and characterized whether lowered Necdin expression affects the response of leukemia-initiating cells to chemotherapy or radiotherapy. MR: This study seeks to understand how Necdin functions in normal and leukemic stem cells, which may lead to innovative clinical applications and benefit those military personnel impacted by the disease.	*Publications: 11* *Presentations: 19* *Funding obtained: 4* *Employment: 1 (PI promoted to Associate Professor)*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
CA130124 $362,178 Pending Closeout	Magee/ Washington University	Temporal Changes in FLT3-ITD Regulation of Stem Cell Self-Renewal and Leukemogenesis	RP: To test whether a receptor tyrosine kinase FLT3-ITD depletes hematopoietic stem cells; to test whether fetal and adult hematopoietic progenitors have different FLT3-ITD-driven signal transduction mechanisms and gene expression; and to test whether ectopic Lin28b expression impedes FLT3-ITD-driven depletion and leukemogenesis. MR: Service members have more risk for exposure to mutagens than civilians; therefore, it is important to understand how the developmental history of a given leukemia will influence its genetic makeup and response to therapy.	*Publications: 1* *Presentations: 3*
CA120212 $417,600 Pending closeout	Cheloufi/ 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 a broad impact on the understanding of cancer development and identification of novel cancer drug targets, which will lead to a better quality of life for Service members and their families.	*Presentation: 4* *Funding obtained: 1 grant* *Publication: 2*
Blood Cancer				
CA130445 $465,000 closed	Jamieson/ University of California, San Diego	Identification of Novel RNA Editing Biomarkers of Human Leukemia Stem Cell Generation	RP: To test the hypothesis that foreign nucleic acid sensing and editing pathways, such as ADAR1, are activated during acute myeloid and lymphoid leukemia propagation as a result of retention of viral genetic material in dormant stem cells. MR: This research will broaden our understanding of risk factors for blood cancer progression and therapeutic resistance in military personnel. New therapeutic strategies could be designed to protect against carcinogenic infectious agents in military environment.	*Publication: 4* *Presentations: 26* *Patents: 1 provisional patent application, 1 PCT patent application* *Funding obtained: 5 grants*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
CA130155 $482,404 Pending Closeout	Atchison/ University of Pennsylvania	YY1 Control of AID-Dependent Lymphomagenesis	RP: To study the role of the transcription factor YY1 in B-cell lymphomagenesis or disease progress. MR: Vietnam War Veterans have a greatly increased risk of Hodgkin's lymphoma (HL), non-Hodgkin's lymphoma (NHL), and chronic lymphocytic leukemia, and many of these cancers initiate due to activation-induced cytidine deaminase activity. Additionally, children of Vietnam War Veterans have an increased risk of developing acute myeloid leukemia.	*Publications: 2*
Colorectal Cancer (CRC)				
CA100111 $313,725 Closed	Jessup/ National Cancer Institute	Inhibition of Embryonic Genes to Control Colorectal Cancer Metastasis	RP: Confirmed that NANOG is a significant prognostic factor as it is expressed in the majority of primary human colon carcinomas. Determined that NANOGP8 inhibition induces apoptosis through inhibition of MCL-1. Also showed that vector-delivered shRNA to NANOGP8 can inhibit BCL-2 and BCL-XL to kill CRC cells. MR: CRC is the second highest cause of cancer-specific mortality in the US population. Approximately 50% of military personnel and dependents who are diagnosed with colon or rectal carcinoma will die of the disease.	*Publications: 2* *Presentations: 7* *Patent: 1 application*
Colorectal Cancer (CRC)				
CA100512/P1 $1,076,301 Closed	Eckhardt; Tan/ University of Colorado Denver	Collaborative Model for Acceleration of Individualized Therapy of Colon Cancer	RP: Three novel anti-cancer agents have been identified to develop predictive classifiers using preclinical CRC 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.	*Publications: 3* *Presentations: 8*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
CA100879 $592,307 Closed	Ellis/ University of Texas MD Anderson Cancer Center	Microenvironmental Influence of Endothelial Cells on Colorectal Cancer Stem Cell Phenotype	RP: Study of the interactions of inflammation, endothelial cells, cancer stem cells (CSCs), and chemoresistance development. Identified and confirmed that soluble JAG1, a paracrine factor of endothelial cells, regulates CSC phenotype in CRC cells by secreting soluble Jagged-1 via ADAM17 proteolytic activity, leading to Notch activation in CRCs. Found that macrophages had a direct CSC-promoting effect that is not mediated by JAG1. MR: The understanding of critical pathways to resistance will support military cancer treatment of Service members and their families.	*Publications: 2 (1 in Cancer Cell)* *Funding obtained: 1*
CA110130 $364,800 Pending Closeout	Yue/ University of Notre Dame	Proteomic Analysis to Identify Functional Molecules in Drug Resistance Caused by E-Cadherin Knockdown in 3D-Cultured Colorectal Cancer Models	RP: A study investigating whether CDH1, a gene encoding a cell-to-cell adhesion protein, drives the connection between drug resistance and metastasis using 3D cultures of CRCs. Using this culture method, knockdown of CDH1 resulted in marked resistance to three of four chemotherapeutic agents tested, thus supporting the claim that reduced CDH1 expression will help cancer cells acquire drug resistance. MR: CRC is the second highest cause of cancer-specific mortality in the general public and military population.	*Publications: 2* *Presentations: 8*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Colorectal Cancer (CRC)				
CA111002 $293,000 Pending Closeout	Mohamadzadeh/ University of Florida	Reprogramming Intestinal Immunity by Novel *L. acidophilus* Strains Results in Protective Immunity against Colon Cancer	RP: Aims to identify critical gene products of *Lactobacillus acidophilus* bacteria that will induce an innate immune response and consequent dampening of pro-inflammatory immune responses within the colon. Revealed that cell surface protein SlpA can protect mice from induced colitis and mitigate polyp formation within a model of hereditary polyposis. This protein plays a critical role in immune regulation in mice by initiating innate immune response through its receptor SIGNR3, which has an orthologous protein in humans. MR: Inflammation and cancer are major debilitating illnesses among military beneficiaries. This work will set the foundation for the development of effective preventions and treatments of these illnesses within the gastrointestinal tract.	*Publications: 10* *Patent: 1* *Funding obtained: 2*
CA110261 $318,000 Closed	Potts/ University of Texas Southwestern Medical Center at Dallas	Role of Germline MAGE Cancer-Testis Antigens in Colorectal Cancer	RP: To investigate the role of MAGE cancer-testis antigens as oncogenes driving cell transformation and tumorigenesis in CRC. Findings defined the oncogenic potential of the MAGE gene family and identified specific genetic contexts and signaling pathways involved during cell transformation. Identified three distinct mechanistic classes of oncogenic MAGEs and mechanistically showed how specific MAGE cancer-testis antigens exert oncogenic activities. MR: CRC is the second highest cause of cancer-specific mortality in the general public and military population.	*Publications: 3 (2 in Cell)* *Presentations: 4* *Funding obtained: 1*
CA110495 $341,040 Closed	Kufe/ Dana-Farber Cancer Institute	Targeting of the MUC1-C Oncoprotein in Colitis-Associated Colorectal Cancer	RP: To explore the mechanisms responsible for the progression of inflammatory bowel disease to CRC for new strategies for drug development. Results indicated that MUC1-C is important mechanistically as a link between intestinal inflammation and CRC progression and represents a potential therapeutic target. MR: CRC is the second highest cause of cancer-specific mortality in the general public and military population.	*Publications: 1*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Colorectal Cancer (CRC)				
CA120198 $374,403 Pending Closeout	Roper/ Tufts Medical Center	The Role of Akt Isoforms in Colorectal Cancer	RP: A study to determine the role of Akt, a protein known to influence cell growth and replication, in the malignancy of CRC. Results suggest that Akt isoforms are independently important for colorectal carcinogenesis in vivo and Akt target proteins play an important role in colorectal cell growth and migration within CRC cell lines. MR: CRC is the third most common cause of cancer in men and second most common cause of cancer in women worldwide, with nearly 1.2 million new cases yearly, and the third leading cause of cancer-related mortality, with approximately 600,000 deaths each year. Therefore, CRC has a significant impact on the health of many of the 21.9 million US military Veterans, as well as their families.	*Funding obtained: 2*
CA120206 $238,515 Closed	MacNeill/ Wake Forest University Health Sciences	Electrically Conducting Polymer Nanoparticles to Selectively Target and Treat Metastatic Colorectal Cancer	RP: Aims to synthesize a new nanoparticle-drug conjugate for targeted photothermal ablation of CRC and demonstrate its therapeutic potential in mice. Development of near-infrared phototherapy using electrical conducting polymer nanoparticles to treat colorectal cancer. Demonstrated that a low band gap D-A conjugated polymer P3 that absorbs in the NIR (~800 nm) can be fabricated into spherical nanoparticles (nano-P3) using Pluronic F127 as a soft template. MR: Only 58% of military men and women who should be screened for CRC have been screened. This number is low compared to the general population and contributes to the fact that CRC is one of the most common forms of cancer among active military personnel.	*This Visionary Postdoctoral Award ended early as the PI secured a permanent position at L'Oreal USA (New Jersey)*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Colorectal Cancer (CRC)				
CA120261 $363,411 Closed	LaBarbera/ University of Colorado Denver, Anschutz Medical Campus	Novel Antimetastatic Agents for the Treatment of Drug-Resistant and Metastatic Colon Cancer	RP: A study to develop analogues to a natural product that inhibits gene expression patterns that promote metastasis. Using rational drug design based on the 3D structure of the target protein, TopoIIa, compounds were synthesized and tested for antitumor activity in vitro and in vivo. From the initial cohort of compounds, one derivative showed inhibition of TopoIIa activity and increased efficacy on in vivo tumor growth as compared to the original lead compound. 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.	*Publications: 5* *Presentations: 18* *Patent: 1*
CA120296 $379,200 Pending Closeout	Kizhakke Mattada/ University of Virginia	Functional Characterization of CENP-A Post-Translational Modifications in Chromosome Segregation	RP: A study to decipher the pathway that leads to epigenetic modification of CENP-A and to determine the function it plays in chromosome segregation. Results suggest that CENP-A α-amino tri-methylation is a crucial post-translational modification in maintaining high fidelity of chromosome segregation and that any defect in this modification may result in aneuploidy and cancer. The research has shown that CENP-A is methylated by NRMT1 both in vitro and in vivo and occurs throughout the cell cycle. The methylation was found to contribute to cell survival, with its absence resulting in senescence, a response dependent on the p53 pathway. Loss of both p53 expression and CENP-A methylation resulted in significantly higher percent of cells with multipolar spindle, a contributing factor to aneuploidy and cancer. MR: CRC is the second leading cause of cancer death in the United States. This study could potentially lead to new targets for CRC treatment and reduce cancer burden among military beneficiaries.	*Presentations: 9*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Colorectal Cancer (CRC)				
CA120342 $417,600 Pending Closeout	Sebastian/ Massachusetts General Hospital	Role of SIRT6 in Metabolic Reprogramming during Colorectal Carcinoma	RP: Aims to elucidate the role of the chromatin factor SIRT6 as a key regulator of glucose metabolism in the context of CRC. Results have demonstrated that SIRT6 acts as a potent tumor suppressor in CRC by controlling glucose metabolic programming, suggesting that targeting glycolysis may provide an approach to modulate cancer growth in tumors with low SIRT6 levels. Using two mouse models and an in vitro intestinal organoid system, the researchers found that a lack of SIRT6 increases the number and activity of intestinal stem cells, indicating that enhanced glycolytic metabolism in the absence of SIRT6 drives intestinal tumorigenesis via an increase of tumor initiating cells. MR: Understanding the metabolic reprogramming in CRC can offer an alternative path to therapeutic development and benefit military personnel impacted by CRC.	*Publications: 4* *Presentations: 1* *Employment: 1 (PI accepted a Group Leader position)*
CA120403 $373,200 Pending Closeout	Shah/ University of Michigan Ann Arbor	The Role of the Noncanonical NF-κB Pathway in Colon Cancer	RP: A study to determine the association of the NF-κB2 pathway and hypoxia in inflammation-associated colon cancer progression. Results suggest that NF-κB2 signaling does play an important role in modulating intestinal inflammation. Inhibition of this pathway shows a decreased number of cells responsible for immune tolerance in the intestine, suggesting that this pathway is a key player in dampening immune response and avoiding tissue damage due to aberrant inflammation. MR: This study will identify new targets for the development of therapeutics for CRC, which could benefit military personnel impacted by CRC.	*Presentations: 1*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Colorectal Cancer (CRC)				
CA130460 $388,800 Pending Closeout	Lee/ Johns Hopkins University	Role of TRAIL Signaling through the Development of Carcinogen-Induced Colorectal Cancer	RP: To discover TRAIL family biomarkers that can serve to predict and prognose colitis-associated colon cancer by investigating the role of TRAIL signaling across different stages of cancer development induced by chemical carcinogenesis. Mouse models of colitis-induced CRC were established revealing that TRAIL receptors showed differential expression at various stages of disease among affected tissues. Furthermore, these receptors show similar dysregulation within CRC patient tissue. The utility of long-lived TRAIL as a CRC therapeutic agent was also examined and in vivo studies show that in IBD-induced CRC mouse models, TRAIL administration has anti-fibrosis, anti-inflammatory, and anti-cancer effects. MR: As Warfighters are at risk of developing environmental diseases, the understanding and identifying of novel biomarkers at different stages of developing CRC will improve the success of preventive screening.	*Publication: 2* *Presentations: 5* *Patents: 3* *Funding obtained: 1 grant*
CA130575 $543,815 Pending Closeout	Rauscher/ Wistar Institute	Control of Colon Cancer Progression by the Colon Microbiome	RP: To examine how NLEE, a bacterially encoded virulence effector protein, induces genomic instability and contributes to the development of colon cancer. Through detailed structural analysis of the protein by crystallization, the PI has established that NLEE contains a unique methylated DNA binding configuration. Computational docking experiments also illustrate the mechanism of NLEE binding-site recognition. This work has helped to identify the mechanism of NLEE action, information that could be leveraged to selectively target NLEE and understand how this protein mediates innate immunity changes. MR: Military personnel can be exposed to noxious pathogens that invade the gut and have long-term influences on colon cancer development and progression.	*Publication: 1* *Presentation: 1*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Genetic Cancer				
CA093054 $113,319 Closed	Lantz/ 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 health risk for Service members. Project included interactions with viral infections, which may lead to long-term health consequences such as cancer development. Found that JP-8 alone did not cause reactivation of Epstein-Barr virus (MHV-68), yet the combination of tungsten and other environmental agents with in utero exposure was able to prime the immune system for aberrant response to infectious agents. MR: Military personnel encounter environmental exposures related to their service that risk long-term healthcare issues, e.g., leukemia clusters.	*Publications: 1* *Presentations: 2* *Employment : 3*
CA093111 $115,500 Closed	Yennu-Nanda/ University of Texas MD Anderson Cancer Center	Role of Melanin in Oncogenesis	RP: Study tested hypothesis that melanin itself can cause melanoma. Results showed induction of excessive melanin production leads to changes in gene expression profiles dependent on skin type and suggest that long-term melanin induction may increase the transformation of melanocytes with low basal melanin levels as compared to those with high basal levels. MR: The prevention and early diagnosis modalities for skin cancers will be of immense benefit to US Soldiers on the frontlines, and in theater where high ultraviolet exposures increase risks.	*None*
CA093139 $559,548 Closed	Cao/ Clemson University	New Protein Modification under Nitrosative Stress	RP: Reactive nitrogen species leads to unstable DNA and carcinogenesis. Treatment of endonuclease V resulted in decreased DNA repair activity. MR: Explosions and blasts occurring in battlefield intensify the contacts of military personnel with gaseous reactive nitrogen species and may inflict acute and chronic impact on the health of military personnel.	*Publications: 4*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Genetic Cancer				
CA093155 $109,875 Closed	Wallis-Schultz/ 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. These genes and their pathways could then be targeted to enhance resistance, treat exposure, improve radiation therapy for those with cancer, or serve as diagnostic or pharmacogenetic biomarkers. 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.	*Publications: 1*
CA093176 $111,301 Closed	Su/ Drexel University	Development of a Genetic Urine Test Using a Padlock-Mediated Microarray for Colon Cancer Screening	RP: Development of a non-invasive, genetic-based CRC biomarker screen using a padlock-mediated microarray to analyze urine. The screen was able to detect a promising CRC DNA marker, the aberrant hypermethylation of the vimentin gene, in the urine of patients with CRC through a blinded study. 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 healthcare costs to the military.	*Publications: 2* *Patent: 1* *Presentations: 1*
CA093193 $109,125 Closed	Elble/ Southern Illinois University	A Novel Therapy for Metastatic Melanoma	RP: Study of the CLCA2 tumor suppressor as a gene therapy candidate for the prevention and treatment of melanoma. Demonstrated that restoration of CLCA2 expression is lethal to melanoma cells. MR: Deployment to areas of high UV exposure puts Service members at increased risk for the development of melanoma and other skin cancers.	*Presentations: 1*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Genetic Cancer				
CA093204 $109,399 Closed	Yusuf/ University of Alabama at Birmingham	Role of p16/INK4a in Ultraviolet Radiation-Induced Inflammation and Photocarcinogenesis	RP: To study the role of p16 in UVB radiation-induced inflammation and skin tumor development. Results indicate that p16/INK4α deficiency does lead to inflammation and associated cutaneous tumor development. MR: Deployment to areas of high UV exposure puts Service members at increased risk for the development of melanoma and other skin cancers.	*Presentations: 1*
CA093257 $96,750 Closed	Chen/ 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. Determined that there is a stable baseline of serum miRNA profiles that can allow for the possible detection of changes associated with radiation-induced lymphoma. 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.	*Presentations: 1*
CA093269 $115,875 Closed	Ongkeko/ 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 cells. Determined that long-term nicotine exposure generates cells with cancer stem cell-like properties that were demonstrated to have a greater capacity for survival with a higher tendency towards invasion. This suggested that nicotine could play a crucial role in the development of tobacco-induced cancers by regulating stem cell characteristics through epithelial-to-mesenchymal promoting of microRNA-mediated pathways. MR: Military personnel have a higher level of cigarette smoking than the general population. Nicotine and tobacco smoking is a risk factor for head and neck cancer.	*Publications: 2* *Funding obtained: 1*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Genetic Cancer				
CA093337 $114,500 Closed	Kitlinska/ 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 have been demonstrated in mouse models of multiple cancer types. MR: Understanding the role of post-traumatic stress disorder and chronic stress in potential cancer development in Veterans is an important area of research.	*Publications: 1* *Presentations: 2*
CA093377 $383,315 Closed	Armani/ 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 Service members encounter. PI demonstrated sensor design and instrument design, surface chemistry of labeling, and detection of methylated DNA. MR: Radiation exposure poses high risk in military populations.	*Publications: 4* *Presentations: 11* *Funding obtained: 2* *Degrees obtained: 1 Ph.D. awarded*
CA093395 $560,148 Closed	Brooks/ 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 showed that UV radiation of extracellular matrix 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 exposure puts Service members at increased risk for development of melanoma and other skin cancers.	*None*
CA093415 $428,999 Closed	Hu/ 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 provides direct link between chronic stress and tumorigenesis in mouse models. Major findings: chronic stress promotes IR-induced tumorigenesis; chronic stress elevates glucocorticoids, negatively regulates p53 function, and promotes tumorigenesis. MR: Understanding the role of chronic stress and radiation exposure for potential cancer development in Veteran population has significant military relevance.	*Publications: 7 (including one in Nature Communications)* *Presentations: 2* *Funding obtained: 4*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Genetic Cancer				
CA093417 $404,299 Closed	Yusuf/ University of Alabama at Birmingham	Regulation of Ultraviolet Radiation-Induced Cutaneous Photodamage and Nucleotide Excision Repair by Toll-Like Receptor-4	RP: 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 in TLR4 knockout mice. MR: Deployment to areas of high UV exposure puts Service members at increased risk for development of melanoma and other skin cancers.	*Publications: 1* *Presentations: 2*
CA093422 $404,849 Closed	Jimeno/ 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. Demonstrated feasibility of engrafting human tumors on humanized mice. The humanized and non-humanized tumor expression profiles will be made available to the public. MR: Advancing genetic research has a direct application to active, reserve, and retired U.S. Service members and their families, because 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.	*Publications: 2* *Patent: 1 application* *Employment: 2*
CA093492 $657,517 Closed	Testa/ Fox Chase Cancer Center	Role of the Inflammasome in Asbestos-Induced Mesothelioma Formation	RP: Study of the role of NALP3 inflammasome and the development of mesothelioma due to asbestos exposure. Demonstrated the genetic link between asbestos-associated inflammation and development of malignant mesothelioma. Found targeting IL-1β signaling with IL-1R antagonist results in delayed asbestos-induced MM onset and progression. MR: Asbestos exposure was widespread among Naval personnel even after the 1980s. Malignant mesothelioma has a long lag time of 20-40 years from initial exposure to diagnosis of the disease. Long-term risk of mesothelioma development following asbestos exposures is critical for US Veterans and active military.	*Publications: 1* *Funding obtained: 1*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Genetic Cancer				
CA093544 $653,132 Closed	Cantor/ 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: Identified 5'UTR mutations in ANKRD26 gene as a novel cause of leukemia predisposition and thrombocytopenia in humans. Identified a role of 5'UTR in DNA repair and chromosome segregation and connected it to two leukemia factors, Menin and MLL. MR: Advancing genetic research has a direct application to active, reserve, and retired US military personnel and their families as a military lifestyle entails potential exposure to carcinogens known or presumed, chemical and physical/ radioactive in nature, both in training and in deployment, and related to equipment utilization and/or combat.	*Presentations: 3* *Funding obtained: 1*
CA093566 $423,038 Closed	Dai/ Oregon Health & Science University	Regulation of c-Myc mRNA by L11 in Response to UV and Gamma Irradiation	RP: Demonstrated that ribosomal protein L11 regulates c-Myc and elucidated the mechanism of ribosomal biogenesis and c-Myc activity under radiation stress conditions. MR: Exposure to environmental hazards in military personnel is associated with increased cancer risks. Studies of hazardous exposures that may cause damage to DNA and long-term healthcare issues such as cancer are beneficial to military personnel.	*Publications: 6* *Presentations: 1* *Employment: 1*
CA093573 $449,979 Closed	Majeti/ 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 (therapy-related acute myelogenous leukemia/therapy-related myelodysplastic syndrome) induced by alkylating agents or ionizing radiation. Established a mouse model of radiation-induced t-AML/t-MDS. 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.	*Publications: 1*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Genetic Cancer				
CA093588 $631,258 Closed	Tsao/ Massachusetts General Hospital	Governance of Cutaneous Photocarcinogenesis by Chronic UVA-Exposed Dermal Fibroblasts	RP: Created a co-culture system and demonstrated that UVA irradiation increased oxidative stress. Confirmed a bystander transmission of reactive oxygen species from the fibroblast target to neighboring non-irradiated cells. MR: Melanoma and other skin cancers represent a significant disease burden to the US military. Military personnel are at risk for higher UV radiation exposures and melanoma development and other skin cancers.	*Publications: 1*
CA093616 $659,431 Closed	Kemp/ 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. Showed that in utero irradiation leads to reduced body weight in young adult mice, which is transmitted through the maternal line to a subsequent generation. Also showed that in utero irradiation leads to increased incidence of lung tumors in susceptible mice. MR: Military personnel are at risk for radiation exposures (UV and gamma) and development of cancers.	*None*
CA100459/P1 $1,201,983 Closed	Moritz; Foltz (Cobbs)/ 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 tools to find relevant biomarkers for novel approaches to the study of all cancers; technical development of whole genome sequencing and quantitative assays. Generated Glioblastoma cell lines from resected human tumor samples to allow for the study of cell type differentiation to define new molecular targets. Completed whole genome sequencing for two Glioblastoma patients and their families. Also completed the proteomic characterization of tumor development to establish diagnostic signature panels. MR: Technological advances supported by the military increase the ability of military medicine to answer the needs of Service members and their families.	*Publications: 4* *Patent: 1*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Genetic Cancer				
CA100545 $571,819 Closed	Broome/ 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. An NIRF-EGF peptide probe was synthesized with a high affinity for EGFR and specific accumulation in cells overexpressing EGFR. Validated that uptake of an EGFR-targeted complex in an orthotopic mouse brain tumor model correlated with upregulated EGFR expression. MR: Technological advances supported by the military increase the ability of military medicine to answer the needs of Service members and their families.	*Publications: 2* *Presentations: 23* *Employment:1*
CA120215 $417,501 Closed	Gutierrez/ Children's Hospital, Boston	Zebrafish Functional Genetics Approach to the Pathogenesis of Well-Differentiated Liposarcoma	RP: Examined oncogenes that contribute to well-differentiated liposarcoma in a zebrafish model. The PI found that FRS2 knockdown, not the hypothesized overexpression, promotes proliferation. Other results showed that expression of CDK4 or HMGA2 in zebrafish led to tumor formation. MR: Exposure to herbicidal agents and radiation predispose one to soft-tissue sarcomas. Development of effective therapies for sarcoma will benefit military Service members and Veterans.	*Presentations: 2*
Kidney Cancer				
CA100587 $454,900 Closed	Singamaneni/ Washington University	Label-Free, Point-of-Service Assay for Non-invasive Detection of Kidney Cancer	RP: Study to develop a urine test for kidney cancer. Demonstrated that a 3D surface-enhanced Raman scattering substrate was two orders of magnitude more sensitive as compared with planar 2D substrate. Also demonstrated that the detection limit of AQP1, a urinary biomarker for kidney cancer, is 10 ng/ml. Created a novel biosensing platform in the form of bioplasmonic paper with a detection capability of 20 ng/ml for model bioanalytes. Developed an approach called bioplasmonic calligraphy to write biofunctionalized nanostructures on paper substrates. 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.	*Publications: 15* *Presentations: 12* *Funding obtained: 2*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Kidney Cancer				
CA101070 $115,875 Closed	Wang/ University of California, San Francisco	Non-invasive Assessment of Renal Tumor Aggressiveness Using Hyperpolarized 13C MR	RP: Development of imaging tools to discriminate between indolent and aggressive renal cancers (RC). Demonstrated the feasibility of using ^{13}C pyruvate magnetic resonance to differentiate metastatic RC from localized RC. Renal cancer cell lines were metabolically characterized to study aggressiveness by evaluating their lactate and pyruvate flux. The study showed that metastatic RC cells have an increased export of hyperpolarized lactate to the extracellular space as compared with localized cells, suggesting that lactate production and export assessment using clinically translatable hyperpolarized probes could serve as a non-invasive tool in characterizing renal tumor aggressiveness. 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.	*Funding obtained: 2 (including a PRCRP Visionary Postdoctoral Award [CA110032 - Sriram])*
CA110032 $239,971.56 Closed	Sriram/ University of California, San Francisco	Hyperpolarized ^{13}C MR Markers of Renal Tumor Aggressiveness	RP: Established model systems of renal cell carcinoma (RCC) to study tumor metabolism using hyperpolarized carbon magnetic resonance. Demonstrated that there is increased lactate production in renal tumors and increased lactate efflux in 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.	*Publications: 5* *Presentations: 5* *Employment: 1*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Kidney Cancer				
CA110769 $296,000 Closed	Frisch/ West Virginia University	Role of Grainyhead in Kidney Cancer	RP: Study of Grainyhead-like-2 (GRHL2), a transcription factor involved in kidney development, to determine its role as a tumor suppressor for renal cell carcinoma and how it prevents RCC progression. Results suggest that GRHL2 expression is highly protective against clear cell RCC by acting as a suppressor of the transcriptional activation function of p300, a protein required for oncogenic epithelial-mesenchymal transition. 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.	*Publications: 1*
CA120409 $370,143.11 Closed	Shen/ 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 in a RCC mouse model. Initial results indicate that tumor cell vaccines can successfully prevent tumor growth in an aggressive orthotopic RCC mouse model. MR: Service members have higher risk of developing kidney cancer due to deployment-related exposure to environment hazards.	*Presentations: 1* *Employment: 1 (The PI was promoted from postdoctoral fellow to Assistant Professor)*
Listeria Vaccines				
CA100463 $543,200 Closed	Chung/ Memorial Sloan Kettering Cancer Center	Evaluation of Immune Responses Mediated by Listeria-Stimulated Human Dendritic Cells: Implications for Cancer Vaccine Therapy	RP: The study demonstrated that *Listeria* infection induced monocyte-derived dendritic cell (moDC), dendritic cell (DCs), and Langerhans cell maturation and activation, leading to T-cell proliferation. These findings confirmed that *Listeria* could stimulate an immune response and potentially serve as a DC vaccine adjuvant. Findings also support the role of Listeria in augmenting the immunity of moDCs, the most commonly used DC in clinical trials, to optimize DC-based cancer vaccines. MR: The development of immune-enhanced technology will benefit military medicine from cancer to infectious diseases (a main exposure risk in deployed military populations).	*Publications: 1*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Listeria Vaccines				
CA110297 $296,000 Closed	Bahjat/ Providence Portland Medical Center	Synergy of SOCS-1 Inhibition and Microbial-Based Cancer Vaccines	RP: Study examined whether induction of negative regulators of inflammation, such as SOCS-1, limit the potency of the tumor-specific immune response. PI tested the utility of combining SOCS-1 inhibition and a *Listeria monocytogenes*-based cancer vaccine on the antitumor effect in mice. Demonstrated that targeting SOCS1 function in *Listeria*-infected cells does improve the magnitude of elicited T-cell responses. MR: Melanoma has been shown to be an immunogenic malignancy, whose incidence has tripled within the last two decades. US troop deployment to areas with intense daily sun exposure will unfortunately increase the risk of melanoma in these Soldiers. The development of a next-generation vaccine for the treatment of malignant melanoma should therefore be of interest to the military.	*None*
Melanoma/Skin Cancer				
CA093370/P2 $1,188,381 Pending Closeout	Kashani-Sabet; Leachman/ California Pacific Medical Center; University of Utah	Molecular Determinants of Melanoma Susceptibility and Progression	RP: Development of a melanoma risk prediction model in US military population. Completed preparation for sample analysis. Obtained permission to access DoD Automated Central Tumor Registry database. Submitted query to database. Sample analysis in progress. MR: Deployment to areas of high UV exposure puts Service members at increased risk for development of melanoma and other skin cancers. Study directly relates to military population and risk.	*None to date*
CA093471/P1 $1,187,984 Closed	Hernando; Osman/ New York University School of Medicine	Altered microRNAs in Melanoma Brain Metastasis	RP: Demonstrated that addition of miRNA expression signature to the current staging criteria improves ability to predict development of brain metastasis; it improves the melanoma clinical management; identified two miRNA whose loss promotes metastasis; and identified one miRNA suppresses metastasis. 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.	*Publications: 5* *Presentations: 3* *Funding obtained: 1*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Melanoma/Skin Cancer				
CA093473/P1 $1,196,001 Closed	Halaban; Brash; Bosenberg/ Yale University	UVL, ROS, Pigmentation, Genetic Predisposition, and Epigenetic Gene Silencing in Melanoma	RP: Study of the linkage between reactive oxygen species, genetic and epigenetic changes, and UV radiation leading to melanoma development. Found a "photochemistry in the dark" phenomenon: DNA damage by UV light continued after 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.	*Publications: 5* *Degrees obtained: 2 (1 Ph.D. awarded and 1 M.S. awarded)*
CA100039 $561,626 Closed	Antony/ University of Maryland, Baltimore	Mechanisms of Relapsing Cancer and the Origin of Melanoma-Specific Regulatory T Cells	RP: Study of immunosuppression and melanoma development. Found a more complexed role of T_{reg} cells in melanoma relapse. Showed that T_{reg} cells prevent treatment of relapse and also that T effector cells become exhausted and can be rescued by antibody therapies to chronic inhibitory receptors. MR: The high exposure to UV radiation to military personnel during deployment is associated with increased risk for melanoma.	*Publications: 2* *Funding obtained: 2*
CA100311 $581,250 Closed	Aplin/ Jefferson Medical College	Role and Regulation of FOXD3 in Mutant B-RAF Melanoma	RP: Established systems to analyze response of melanoma xenografts to RAF inhibitors in vivo and showed down-regulation of FOXD3 targets enhanced the effects of RAF inhibitors in vivo. Data also indicate that ERBB3 signaling is important in response to RAF inhibitors in vitro and 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.	*Publications: 2* *Presentations: 6* *Funding obtained: 2*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Melanoma/Skin Cancer				
CA101019 $116,250 Closed	Aplin/ Jefferson Medical College	Novel Mechanisms of Resistance to B-RAF Inhibitors in Melanoma	RP: Study of novel mechanisms of chemotherapy resistance to RAF inhibitors and melanoma treatments. Developed a system to quantify changes in ERK1/2 signaling in tumor cells with elevated activity and showed that mutant NRAS is sufficient to confer resistance to RAF inhibitors and that mutant NRAS-resistant cells alter their signaling connections in response to RAF inhibitor. 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.	*Publications: 2* *Patent: 1* *Funding obtained: 1*
CA101118 $114,750 Closed	Serafini/ 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 antigen presenting cells to generate effective tumor immunity. Confirmed genetic modification via shRNA of tumor-educated myeloid cells alters the immune system by creating an antitumor immune response able to restrain the growth of melanomas. Developed an IL4-PAMAM dendrimer platform able to target tumor-educated myeloid cells and myeloid-derived suppressor cells in vivo. 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.	*Presentations: 1* *Funding obtained: 1 (BCRP Idea Award)*
CA101202 $130,498 Closed	Libermann/ Beth Israel Deaconess Medical Center, Boston	Testing New Drugs for Treatment of Melanoma Patients Applying Connectivity Map Database Analysis with Melanoma Gene Signatures	RP: To identify drugs for treating metastatic melanoma through the use of meta-analysis of melanoma transcriptome data to generate a metastatic melanoma gene signature. This gene signature was then applied to the Connectivity Map Database of drug gene signatures, resulting in identification of several drugs that are strong inducers of apoptosis in melanoma cell lines. MR: Military personnel are at risk for UV radiation exposures and development of cancers.	*None*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Melanoma/Skin Cancer				
CA110011 $240,000 Closed	Ransom/ University of Colorado 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. This study optimized a new ligation-based method to study DNA modification caused by UV exposure and found that known regulatory domains within the genome, promoters and enhancers, are more susceptible to UV damage. 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, the Middle East region), melanoma can be the most frequent cancer that military personnel will face during their lives.	*Publications: 1* *Presentations: 2*
CA110017 $368,400 Closed	Goding/ University of Maryland, 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. CD4+ T cells from mice with relapsing tumors expressed hallmark indicators of chronic exhaustion, and when the mice were treated for exhaustion, tumors regressed and the markers decreased. 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 US Navy. Military personnel are at risk for UV radiation exposures and development of cancers.	*Publications: 2* *Presentations: 2*
CA110094 $322,849 Pending Closeout	Callahan/ 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: Findings suggest a model where BRAF inhibitors are likely to combine with immunotherapies to generate robust, long-lasting antitumor T-cell responses while MEK inhibitors may compromise the generation of long-lasting T-cell memory. Data support a superior antitumor effect in vivo with BRAFi+CTLA-4 blockade or BRAFi+ PD-1 blockade versus monotherapy. MR: Service members are deployed to areas of high risk and exposure to UV light.	*Publications: 1* *Presentations: 3* *Funding obtained: 1* *Employment:1 (PI was appointed to a faculty position)*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Melanoma/Skin Cancer				
CA110107 $259,200 Closed	Zhang/ Mount Sinai School of Medicine	Insight into Skin Tumorigenesis Highlighting the Function of Epigenetic Regulators in SCC Formation	RP: To dissect the Ezh2 regulatory network that controls skin squamous cell carcinoma (sSCC) formation, focusing on the evaluation of regulatory networks and their mechanisms in control of the early steps of sSCC formation. Observations suggest that Ezh2 may function in multiple ways to form a regulatory network and imply a new and unexpected H3K27me3-independent mechanism. MR: Service members are deployed to areas of high risk and exposure to UV light.	*Publications: 1* *Award ended early due to the PI being offered a faculty position at the Qingdao University of Science and Technology (China)*
CA110183 $313,000 Closed	Marchetti/ 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 (MBM). This study identified SST001 as an anti-heparanase compound that inhibits MBM tumor growth in vivo and established that heparanase activity is a molecular determinant of MBM onset that can be mitigated by treatment with SST001. MR: Malignant melanoma, associated with increased sun exposure, is a cancer type with the most aggressive propensity to colonize the brain. Better understanding of the mechanism of metastasis will lead to treatments that will improve quality of life for those prone to this type of cancer including active military.	*Publications: 1* *Funding obtained: 1 (R01 from NCI)*
CA110338 $296,400 Closed	Bikle/ Northern California Institute for Research and Education	The Tumor Suppressor Actions of the Vitamin D Receptor in Skin	RP: Developed mouse models for the expression of the hedgehog and wnt/beta-catenin pathways to determine if they would alter susceptibility of the VDR null mouse to UVB-induced epidermal cancer. Conducted short UVB exposure studies for most of the developed mouse models. 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. Military personnel are at risk for UV radiation exposures and development of cancers.	*Publications: 7* *Presentations: 1*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Melanoma/Skin Cancer				
CA110396 $327,333 Closed	Faller/ Boston University Medical Campus	Targeting N-Ras as a Therapeutic Approach for Melanoma	RP: To test whether the inhibition or downregulation of PKCδ in human and murine models of melanoma with aberrant activation of N-RAS signaling will cause targeted cytotoxicity in melanoma tumors. Results validate PKCδ as a target and provide proof of principle for the use of PKCδ inhibitors as a strategy to eliminate BRAF mutant melanomas resistant to BRAF inhibitors. MR: Service members are deployed to areas of high risk and exposure to UV light.	*Publications: 3* *Presentations: 1*
CA110462 $289,871 Closed	Zhang/ University of Colorado Denver, Anschutz Medical Campus	Targeting "Dynamic Stemness" of Melanoma by Blocking the NADH-Dependent CtBP Function	RP: To study whether hypoxia, hyperglycemia, and UV irradiation trigger the conversion of melanoma cells by the activation of CtBP-mediated transcription and if blocking its function can be used as a novel therapeutic strategy. Found that CtBP hyperfunction leads to induction of H3K4 demethylase JARID1B protein, a key marker for melanoma self-renewal. Determined that NADH rise induced by hypoxia upregulates JARID1b mRNA levels in melanoma cells. MR: Military personnel are at risk for UV radiation exposures and development of cancers.	*Publications: 1* *Funding obtained: 1 (I01 from the VA)*
CA110602 $284,597 Closed	Hernando/ New York University School of Medicine	Identification of Glycomic Alterations during Melanoma Metastasis	RP: To better understand the changes that occur within the tumor microenvironment that may be triggered by microRNAs released from melanoma cells with specific interest in the sugars present on the surface of cells. Data suggest that microRNA-linked alterations in cell surface sugars may be an early event in the malignant transformation of melanocytes to melanoma. MR: Deployment to areas of high UV exposure puts Service members at increased risk for the development of melanoma and other skin cancers. This study directly relates to military population and risk.	*Publications: 3* *Presentations: 1*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Melanoma/Skin Cancer				
CA110802 $305,000 Closed	Morris/ University of Minnesota, Twin Cities	A Novel Mechanism for the Pathogenesis of Nonmelanoma Skin Cancer Resulting from Early Exposure to Ultraviolet Light	RP: To examine whether stem cells residing within the skin can be provoked to migrating to other tissues upon UV irradiation. Findings support the hypothesis that skin keratinocytes can leave the cutaneous epithelium and enter the blood and bone marrow. Results indicate that the bone marrow may act as a long-lived reservoir of these UV-damaged cells that may be used to repopulate the skin years after damage has occurred. 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.	*Presentations: 1*
CA110823 $308,000 Closed	Bullock/ University of Virginia	Functional Proteomics to Identify Moderators of CD8+ T-Cell Function in Melanoma	RP: This study uses the technique of phage-display to express a library of proteins with the intention of identifying new binding partners of tumor-infiltrating (TIL) T cells. Identified 17 unique agents that selectively bind TIL T cells without cross-reactivity with other lymphocytes. These can be used as new tools for T cell identification and tumor visualization. MR: Service members are at risk for UV radiation exposures and development of cancers.	*Presentations: 3*
CA111032 $305,000 Pending Closeout	Basu/ Ohio State University	Role of Catecholamines in the Regulation of Angiogenesis in Preneoplastic Skin Lesions	RP: A study aimed at determining the role of dopamine receptors and adrenoceptors in skin carcinogenesis. Developed a mouse model of skin carcinogenesis and demonstrated that vascular endothelial growth factor (VEGF)-induced angiogenesis is responsible for the initiation and progression of the disease model. Furthermore, blocking the synthesis of VEGF by treatment with dopamine receptor or adrenoceptor modulators reduced tumor number as well as tumor size in these animals. MR: Service members are deployed to areas of high risk and exposure to UV light.	*Presentations: 6*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Melanoma/Skin Cancer				
CA120099 $400,800 Pending Closeout	Ceol/ University of Massachusetts 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. PI has found that GDF6 is an important component in maintaining a de-differentiated state and that loss of GDF6 expression is what triggers differentiation towards a melanocyte lineage. Thus, presence of GDF6 expression in tumor cells is a way for melanoma cells to co-opt embryonic activities thus preventing differentiation and cell death. 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.	*Publications: 5* *Presentations: 12* *Patent: 1*
CA120161 $417,600 Closed	Wu/ Massachusetts General Hospital	Targeting Palmitoyl Acyltransferases in Mutant NRAS-Driven Melanoma	RP: Development of a new class of palmitoyl acyltransferase inhibitors (PATs) that target N-RAS mutant melanomas. These potent chemical probes were used to identify all PATs expressed in melanoma cells. MR: Military service often requires prolonged outdoor activity resulting in high exposure to ultraviolet light, the leading risk factor for melanoma.	*Publications: 2* *Funding obtained: 2 (R01 from NIDDK, R01 from NCI)*
CA120240 $399,600 Pending Closeout	Yan/ Yale University	Targeting Epigenetic Regulator JARID1B in Malignant Melanoma	RP: Determination of the effects after loss of an epigenetic regulator, JARID1B, on melanoma formation and progression. Found that mitochondrial transcription as well as WNT and mTOR signaling are modified in the absence of JARID1B leading to decreased cell proliferation in melanoma cells. Results have shown that loss of JARID1B delays tumor formation and treatment with newly developed protein-specific inhibitors decreases cancer cell colony formation. MR: Melanoma can be caused by heavy sunlight exposure, such as for Service members in areas like Iraq. Identification of new drug therapies will have significant impact on treatments for those at higher risk of this cancer.	*Publications: 2* *Presentations: 24* *Funding obtained: 2 (both from PRCRP)* *Employment: 1 (PI was promoted to Associate Professor on 1 July 2014)*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Melanoma/Skin Cancer				
CA130184 $585,000 Pending Closeout	Ronai/ Sanford-Burnham Medical Research Institute	Siah1/2 Ubiquitin Ligases in ER Stress Signaling in Melanoma	RP: To determine the significance of the Siah2-hypoxia-ER stress regulatory axis in melanoma development and progression and to evaluate the use of Siah1/2 and ER stress inhibitors as potential therapeutics. Confirmed that Siah2 presence on tumors inhibits immune cell infiltration through an immune checkpoint mechanism, and loss of siah2 expression in melanoma cells could slow down tumor development in vivo. Developed a first-in-class inhibitor for ubiquitin ligases that inhibit "cancer-like" phenotypes within cultured cells. MR: The risk for melanoma development is significantly higher in a younger age group (16-25), making development of new treatments and prevention of melanoma pertinent for active Service members.	*Publications: 3* *Presentations: 9* *Patent: 1*
CA130409 $464,034 Pending Closeout	Abdel-Malek/ University of Cincinnati	Differential Impact of P16 mutations with or without Coexpression of MC1R Mutation on the UV Response of Melanocytes, and Hence on the Risk for Melanoma	RP: To determine the mechanisms by which co-expression of mutations in p16 and loss-of-function allelic variants of MC1R synergistically increase the risk for melanoma. Tested the impact of three mutations in p16 that are present in familial melanoma cases on melanocyte transformation in the absence or presence of non-functional MC1R. Found that heterozygosity for p16 mutations is not enough to affect UV exposure sensitivity within these cells. Results suggest that although p16 mutations are sufficient to cause melanoma in patients, the transformation to cancer does not seem to be due to abnormal melanocyte function. MR: Understanding the tissue biomarkers that predispose populations to melanoma will be of considerable importance for Service men and women stationed in environments with high UV exposure.	*Presentations: 1* *Funding obtained: 2 (both R21s from NCI)*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Melanoma/Skin Cancer				
CA130414 $508,500 Pending Closeout	Bernstein/ Mount Sinai School of Medicine	Identifying Epigenetic Modulators of Resistance to ERK Signaling Inhibitors	RP: To decipher the epigenetic mechanisms underlying melanoma drug resistance by mapping the epigenomic landscape of melanoma cells that have acquired resistance to signaling inhibitors. Research has revealed novel and critical epigenetic regulators of resistance to RAF inhibitors and RAF inhibitors + MEK inhibitors. Loss of function screening has also identified new drivers of RAFi resistance in melanoma cells. MR: Cutaneous malignant melanoma is the most lethal form of skin cancer, arises from the pigment-producing cells known as melanocytes and is mainly due to sun exposure – an environmental influence associated with military exposures.	*None to date*
Mesothelioma				
CA110442 $296,850 Closed	Robinson/ University of Western Australia	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 transformation and tumor development and is inhibited by immunological restraints. Observed that the depletion of Treg cells can significantly enhance antitumor immunity and delay tumor development. Also found that targeted Treg removal in combination with gemcitabine chemotherapy significantly enhanced overall survival in comparison to chemotherapy alone. Observed that asbestos-induced mesothelioma development is slower in mice that lack a functional immune system compared to mice that are immune competent. MR: Initial exposure to the diagnosis of the disease. Long-term risk of mesothelioma development following asbestos exposures is critical for US Veterans and active military.	*Funding obtained: 1*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Mesothelioma				
CA110751 $308,000 Pending Closeout	Sharma/ University of California, 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. Generated three different mesothelioma knockdown cell lines and studied the growth and invasion characteristics of these cells in vitro. Observed reduced tumor growth rate and increased immune cell recruitment with Snail knockdown cell lines as compared to controls, suggesting that Snail is a critical component in the immune modulation of these malignancies. 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.	*None to date*
CA110765 $316,000 Closed	Salgia/ University of Chicago	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 (MPM) and determine the efficacy of some of the PI3K and PI3K/TOR inhibitors in MPM cell culture and mouse models. Results suggest that a combination of drugs is more effective than using each alone in suppressing tumor growth and motility. MR: Asbestos exposure was widespread among Naval personnel even after the 1980s. Long-term risk of mesothelioma development following asbestos exposure is critical for US Veterans and active military.	*Publications: 1* *Presentations: 1*
CA110772 $294,870 Closed	Heasley/ University of Colorado Denver, Anschutz Medical Campus	Targeting Fibroblast Growth Factor Receptor Signaling Pathways in Mesothelioma	RP: To test the hypothesis that co-expression of fibroblast growth factors (FGFs) and FGF receptors create an autocrine growth loop in mesothelioma that promotes cancer growth. Studies support that FGFR1 activation through autocrine FGF2 is a driver of oncogenic growth in a subset of mesothelioma cell lines. Determined that FGFR1 is a novel target for therapeutic intervention in mesothelioma. MR: Long-term risk of mesothelioma development following asbestos exposure is critical for US Veterans and active military.	*Publications: 1*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Mesothelioma				
CA120102 $256,613 Pending Closeout	Klein/ 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. Identified that cell penetrating p16-derived peptides have good potency against CDK4 and act with a synergistic effect when applied in combination with palbociclib. Also shows that palbociclib has an effect on mesothelioma cell proliferation and apoptosis as a single therapy. MR: Mesothelioma often arises in military personnel and Veterans who were exposed to asbestos or asbestos-like materials during routine duties or deployment. Mesothelioma is a highly fatal disease that can affect those exposed to asbestos.	*Publications: 1* *Presentations: 7*
CA120355 $360,000 Pending Closeout	Yang/ University of Hawaii	Mesothelioma: Identification of the Key Molecular Events Triggered by BAP1	RP: Study of the impact of BAP1 on the release of HMGB1 and the effect of BAP1 status on the development of mesothelioma (MM). Results suggest that decreased BAP1 expression reduced sensitivity to asbestos-induced cytotoxicity in both primary human and mouse cells. Remarkably, in vivo investigation into the effect of BAP1 on mesothelioma development found that BAP1+/- mice exposed to low doses of asbestos developed MM at a similar rate as BAP1+/+ mice exposed to 10 times higher doses. Thus, BAP1 is protective against MM development and may be used as a potential marker for MM risk in asbestos-exposed populations. 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, aircraft, ships, and buildings.	*Publications: 9* *Presentations: 10* *Patents: 3* *Funding obtained: 1 (R01 from NCI)* *Employment: 1 (PI was promoted to Associate Professsor)*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Mesothelioma				
CA130248 $508,593 Pending Closeout	Poznansky/ Massachusetts General Hospital	Development of a Novel Immunotherapy for Malignant Mesothelioma that Combines CXCL12/CXCR4 Blockade with a Mesothelin-Targeted Fusion Protein	RP: To develop a novel immunotherapy approach for malignant mesothelioma (MM) that combines CXCR4 blockade with a mesothelioma-targeted immunogenic fusion protein. Developed two new mouse models of MM that allow non-invasive monitoring of tumor growth and progression. The PI tested the combination therapy in vivo for the two mouse models and shows that this treatment not only synergizes the antitumor immune effect but also prolongs mouse survival. MR: Mesothelioma, a cancer induced by respiratory exposure to asbestos, disproportionately affects military personnel. While Veterans represent 8% of the nation's population, they comprise an astonishing 30% of all known mesothelioma deaths that have occurred in the United States.	*Patents: 2* *Licenses: 1* *Presentations: 1*
Non-Invasive Ablation				
CA093108 $114,836 Closed	O'Donnell/ 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 a disease site (non-Hodgkin's lymphoma). Developed immuno-nanomicelles to specifically target tumors and increase the therapeutic index of chemotherapy. Mice treated with encapsulated micelles had a superior antitumor response compared with using vincristine alone. 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.	*Publications: 2*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
CA093166 $134,884 Closed	Gach/ 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. Observed 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. MR: Development of a new treatment modality for tumor ablation may translate to expansive medical methodologies with military benefit.	*Publications: 2* *Presentations: 1* *Funding obtained: 2*
Non-Invasive Ablation				
CA093180 $117,684 Closed	Berdis/ Case Western Reserve University	Gold-Containing Nucleosides as Non-invasive Ablation Agents	RP: Development of gold-containing nucleosides as target agents to potentiate the efficacy of ionizing radiation for maximal tumor ablation. Results positively highlighted the applicability of combining Au(I)-indoles with ionizing radiation as a new strategy to ablate tumors using non-invasive techniques. MR: Technological advances supported by the military increase the ability of military medicine to answer the needs of Service members and their families.	*Publications: 1*
CA093210 $117,000 Closed	Pan/ University of Chicago	Testing Delivery Platforms for New Anticancer tRNA-Based Drugs	RP: Development of killer tRNA nanoparticles as a potential blood cancer treatment. Obtained proof of concept results in blood cancer cells encouraging the continued development of efficient delivery systems. 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.	*Publications: 1*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
CA093389 $598,307 Closed	Torti/ University of Connecticut	Targeted Nanoparticles for Kidney Cancer Therapy	RP: Development of novel optically activated multi-functional nanotubes to target and kill renal cancer cells. Soluble D5-conjugated nanotubes were produced; toxicity of unconjugated nanotubes to kidney cancer cells was tested. Results demonstrated that combination of NIR and nanotubes could successfully inhibit 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.	*Publications: 4* *Presentations: 2*
Non-Invasive Ablation				
CA093453 $670,720 Closed	Panyam/ University of Minnesota, Twin Cities	Targeted Magnetic Hyperthermia for Lung Cancer	RP: Study demonstrated that super paramagnetic iron oxide nanoparticles 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.	*Publications: 4* *Presentations: 15*
Pancreatic Cancer				
CA110076 $368,400 Closed	Lunt/ Michigan State University	Understanding the Warburg Effect and the Metabolic Requirements of Cancer Cells	RP: PI studied role of pyruvate kinase (PK) isoform expression in altered metabolism in pancreatic and blood cancer cells. She created cell lines expressing different isoforms of PK and mass spectrometry-based methods to study them. Using these tools, the PI was able to elucidate the mechanism by which the isoform PKM2 deletion leads to proliferation arrest in normal cells. MR: Higher risk of pancreatic cancer has been shown in populations exposed to pesticides such as Agent Orange. Higher risk of pancreatic cancer in nurses who served in Vietnam has been reported.	*Publications: 5* *Presentations: 8* *Funding obtained: 2 (1 from CDMRP's BCRP)* *Employment: 1 (The PI was promoted from postdoctoral fellow to Assistant Professor as the close of this award.)*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
CA110164 $296,000 Closed	Houchen/ University of Oklahoma Health Sciences Center	Tuft Cell Regulation of miRNAs in Pancreatic Cancer	RP: PI tested the hypothesis that tuft cells are specialized chemosensing cells in the pancreas and that, with the appropriate oncogenic signals, tuft cells may become the cells of origin for pancreatic cancer. Progress to date includes the successful deletion of DclK1 throughout the pancreatic ducts of a transgenic mouse model. MR: Higher risk of pancreatic cancer has been shown in populations exposed to pesticides such as Agent Orange. Higher risk of pancreatic cancer in nurses who served in Vietnam has been reported.	*Publications: 1* *Presentations: 1* *Funding obtained: 1 (R01 from NCI)*
Pancreatic Cancer				
CA110449 $320,000 Closed	Beatty/ University of Pennsylvania	Listeria Vaccines for Pancreatic Cancer	RP: Examination of whether *Listeria* vaccines can overcome the immune suppression associated with pancreatic ductal adenocarcinoma by stimulating antitumor responses able to target both tumor cells and their surrounding microenvironment. Found that *Listeria* vaccines produce little impact on late-stage tumors with an absence of T-cell infiltration into tumor tissue, but do appear to have non-antigen specific anti-stromal effects. MR: Higher risk of pancreatic cancer has been shown in populations exposed to pesticides such as Agent Orange. Higher risk of pancreatic cancer in nurses who served in Vietnam has been reported.	*Publications: 3* *Presentations: 2* *Patent: 1 provisional patent*
CA110530 $241,880 Closed	Solomon/ 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. Metabolites have been measured in fasting serum samples and preliminary analysis has been conducted. 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 nurses who served in Vietnam has been reported.	*None to date*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
CA110535 $310,000 Closed	Yu/ 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. Completed a loss of function genetic screen using a siRNA library of somatically mutated genes. Selected 20 gene candidates for further analysis to determine their activities in DNA replication and damage responses. MR: Higher risk of pancreatic cancer has been shown in populations exposed to environmental agents and pesticides such as Agent Orange.	*Publications: 3* *Presentations: 25*
Pancreatic Cancer				
CA110636 $313,690 Closed	Fletterick/ University of California, 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 pancreatic ductal adenocarcinoma cells (PDAC). Performed computational filtering of over 5 million compounds. Demonstrated that PDAC cells expressing LRH-1 are sensitive to treatments with receptor-specific inhibitors and that growth and proliferation of LRH-1 positive cancer cells could be markedly decreased following such treatments. Sent two compounds to the National Cancer Institute Chemotherapeutic Agents Repository for use in the research community. MR: Higher risk of pancreatic cancer has been shown in populations exposed to environmental agents and pesticides such as Agent Orange.	*Publications: 3* *Presentations: 2* *Funding obtained: 1*
CA110724 $289,988 Closed	Phanstiel/ University of Central Florida	Development of Novel Cancer Therapies that Target Polyamine Metabolism	RP: To determine if sustained polyamine depletion in human pancreatic cells leads to apoptosis so that a combination therapy can be developed using inhibitors of polyamine biosynthesis and transport. Identified a new gene associated with polyamine transport that could serve as a potential biomarker. Combination therapy of new polyamine inhibitors showed efficacy in pancreatic cancer mouse models. MR: Higher risk of pancreatic cancer has been shown in populations exposed to environmental agents and pesticides such as Agent Orange.	*Publications: 5* *Patent: 1 application* *Presentations: 15* *Degrees obtained: 1 Ph.D. awarded*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
CA110731 $340,894 Closed	Corcoran/ 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 inhibited, allow MEK inhibitors to work against K-RAS mutant pancreatic cancer cells. Completed the primary in vitro shRNA drug screen and prioritized the top 100 gene targets for a secondary screen in an orthotopic mouse model of pancreatic cancer. MR: Higher risk of pancreatic cancer has been shown in populations exposed to environmental agents and pesticides such as Agent Orange.	*None to date*
Pancreatic Cancer				
CA110832 $290,720 Closed	Mukherjee/ University of North Carolina, Charlotte	A Novel Association and Therapeutic Targeting of Neuropilin-1 and MUC1 in Pancreatic Cancer	RP: Exploration of the hypothesis that MUC1, a marker of aggressive tumors, is driving metastatic spread by increasing Neurophilin 1 levels within pancreatic tumors. Showed that NRP1 may be an excellent target for treating MUC1-positive, but not negative, pancreatic ductal adenocarcinoma. Developed a novel antibody-anti-angiogenic drug conjugate. MR: Higher risk of pancreatic cancer has been shown in populations exposed to environmental agents and pesticides such as Agent Orange.	*Publications: 1* *Presentations: 1* *Funding obtained: 1 (R15 from NCI)*
CA110994 $388,633 Closed	Sabatini/ 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. Results suggest that intermediates of tryptophan breakdown may be good targets for therapies based upon toxic metabolites. MR: Higher risk of pancreatic cancer has been shown in populations exposed to environmental agents and pesticides such as Agent Orange.	*None to date*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
CA111019 $311,152 Closed	Jacks/ 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 knock down 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. Progress includes the identification and characterization of a reversible K-RAS-independent state as murine cells, both in vitro and in vivo, can survive and proliferate despite persistent K-RAS knockdown. MR: Higher risk of pancreatic cancer has been shown in populations exposed to environmental agents and pesticides such as Agent Orange.	*Presentations: 1* *Funding obtained: 1*
Pancreatic Cancer				
CA111036 $215,325 Closed	Kimmelman/ Dana-Farber Cancer Institute	In Vivo Measurement of Oncogenic KRAS-Dependent Glucose Metabolism in Mouse Models of Pancreatic Cancer	RP: Development of a novel method of measuring incorporation of glucose into pancreatic tumor models to assess where it is metabolized. Goal is to develop a list of critical elevated metabolites and their associated pathways. Using a mouse model of pancreatic cancer, the PI refined methods to label tumors in vivo using ^{13}C glucose. MR: Higher risk of pancreatic cancer has been shown in populations exposed to environmental agents and pesticides such as Agent Orange.	*Publications: 1*
CA120028 $405,600 Pending Closeout	Du/ Cornell University, Weill Medical College	RHAMMB Promotes Liver-Specific Metastasis of Pancreatic Neuroendocrine Tumors	RP: To determine the role of EGFR in RHAMMB (receptor for hyaluronan-mediated motility isoform B) induced liver metastasis and the clinical relevance of RHAMMB in human pancreatic neuroendocrine tumors. Results suggest that RHAMMB induces the liver metastasis of panNETs through EGFR signaling and that RHAMMB is associated with panNET disease progression. MR: Military missions benefit when the military families are healthy and well.	*None to date*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
CA120057 $410,940 Closed	Ting/ Massachusetts General Hospital	Impact of Noncoding Satellite Repeats on Pancreatic Cancer Metastasis	RP: To study the role of RNA satellites in pancreatic cancer genetics, metastasis, and circulating tumor cells. Assessed HSATII in pancreatic circulating tumor cells (CTCs) with results suggesting it as a blood-based early detection biomarker. 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 nurses who served in Vietnam has been reported.	*Publications: 2* *Patents: 1 application* *Presentations: 5* *Funding obtained: 2*
Pancreatic Cancer				
CA120188 $373,200 Closed	Rhim/ University of Michigan	A Novel Mechanism for Post-Transcriptional Regulation in Pancreatic Cancer Progression	RP: To study the RNA-DNA differences (RDDs) in pancreatic pre-cancer and tumor cells and determine the genes in which RDDs occur during cancer progression. Using refined techniques to isolate high-quality RNA for sequencing, and developing a new bioinformatics platform to analyze the data, the PI found widespread RDDs in a mouse model of pancreatic cancer. MR: Pancreatic cancer is one of the most lethal forms of cancer affecting Service members, Veterans, and military beneficiaries and their families.	*Presentations: 15* *Funding obtained: 4 (including being a Co-I on an NIH R01 from NCI)*
CA120412 $349,382 Closed	Nagrath/ University of Michigan, Ann Arbor	Integrated Microfluidic Magnetic CTC Sorter and Enumerator for Early Diagnosis and Management of Pancreatic Cancer	RP: The PI successfully developed an integrated microfluidic magnetic cell sorter and enumerator to separate circulating tumor cells (CTCs) from the blood of pancreatic patients. The device could detect CTCs in 100% of patient samples, and the CTCs could be sorted to an average of 82.5% purity. The high purity level allows for further testing and characterizing of the patient samples, which supports use of this devise in clinical trial design. MR: Higher risk of pancreatic cancer has been shown in populations exposed to environmental agents and pesticides such as Agent Orange.	*Publication: 3* *Presentations: 3* *Funding obtained: 2 (1 R33 from NCI)* *Employment: 2 (PI received tenure and was promoted to Associate Professor)*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
CA130229 $333,878 Pending Closeout	Brooks/ University of Mississippi	Novel Molecular Targets for KRAS Downregulation: Promoter G-Quadruplexes	RP: To define the formation, regulation, and therapeutic potential of identified G-quadruplexes (G4s) within the K-RAS core promoter. The PI characterized the biophysical properties of G4 complexes within the K-RAS promoter and conducted functional studies to describe how the G4 formations influence promoter activity. MR: Pancreatic cancer is one of the most lethal forms of cancer affecting Service members, Veterans, and military beneficiaries and their families.	*Publications: 1* *Presentations: 10*
Pancreatic Cancer				
CA130578 $567,000 Pending Closeout	Tuveson/ Cold Spring Harbor Laboratory	The Early Detection of Pancreatic Cancer in the US Military	RP: To identify serological biomarkers during carcinogen-mediated pancreatic cancer initiation and progression upon exposure to military-relevant environmental carcinogens. After establishing the model systems, preliminary results identified several biomarker candidates that will be validated in future studies. MR: Pancreatic cancer is one of the most lethal forms of cancer affecting Service members, Veterans, and military beneficiaries and their families.	*Publications: 1* *Funding obtained: 2 (R33 from NCI)*
Pediatric Brain Tumor				
CA093469/P1/P2/ P3 $1,786,229 Closed	Gilbertson; Guy; Ellison; Malkin/ St. Jude Children's Research Hospital; Hospital for Sick Children	Molecular-Targeted Therapies of Childhood Choroid Plexus Carcinoma (CPC)	RP: Large throughput screening to study candidate oncogenes and potential drug targets for rare cancers. Validated the overlapping human and mouse genetics and initiated the first whole genome sequencing of CPC. 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. Selected five compounds for preclinical study and demonstrated in vivo efficacy and favorable pharmacology of gemcitabine that can be advanced immediately to clinical trial. MR: Development of cost-efficient screening techniques for rare diseases will benefit military medicine.	*Publications: 2* *Presentations: 10*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Pediatric Brain Tumor				
CA100157 $465,000 Closed	Read/ Emory University	Identification and Characterization of Metastatic Cancer Stem Cells in Medulloblastoma	RP: To identify and characterize cells responsible for metastatic disease in medulloblastoma patients, identify genetic markers that predict metastasis, and find novel molecular targets for therapeutics. Found that smo/smo and ptc +/- primary medulloblastoma could be propagated by CD15+/Math1+ cancer stem cells. Identified a unique protein, Math1, as well as markers and drivers of metastasis as therapeutic targets. 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.	*None to date*
CA100335 $450,843 Closed	Keating/ University of Colorado Denver, Anschutz Medical Campus	Targeting Pediatric Glioma with Apoptosis and Autophagy Manipulation	RP: Confirmed upregulation of autophagy by Mer and Axl shRNA inhibition in several human glioma cell lines. Successful inhibition of Mer and Axl RTK with a commercially available small molecule inhibitor resulted in increased apoptosis, decreased migration, and suppressed tumor growth. Results suggest that Mer and Axl RTK signaling regulates autophagy pathway activation in glioma cells to determine the efficiency of glioma cell killing. MR: The health and welfare of the force are partially determined by the health and welfare of their supportive families. Military missions benefit when Warfighters' families are healthy and well.	*Publications: 4* *Presentations: 3*
CA100469 $531,373 Closed	Zong/ University of Virginia	Social Behavior in Medulloblastoma: Functional Analysis of Tumor-Supporting Glial Cells	RP: Investigation for understanding the crosstalk between glial cells and medulloblastoma. The study found that glial-ablation treatment resulted in complete remission of tumors and such treatment was also effective for late-stage tumors. MR: The health and welfare of the force are partially determined by the health and welfare of their supportive families. Military missions benefit when the Warfighters' families are healthy and well.	*Presentations: 9* *Funding obtained: 1 (R01 from NINDS)*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Pediatric Brain Tumor				
CA100601 $456,583 Closed	Becher/ 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. Generated several diffuse intrinsic pontine glioma mouse models. Identified the transcription factor, pax3, to be significantly upregulated in a diffuse intrinsic pontine glioma (DPIG) model, but not in a cortical glioma model, although both were driven by the same genetic alterations. MR: The health and welfare of the force are determined by the health and welfare of their supportive families. Military missions benefit when the Warfighters' families are healthy and well.	*Publications: 5* *Presentations: 2* *Funding obtained: 2 (1 K02 from NINDS)*
CA100735 $511,136 Closed	Paddison/ 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 and characterized several patient-derived cell lines through gene expression analysis and patient-specific gene mutations and has begun to identify candidate therapeutic targets. MR: The health and welfare of the force are partially determined by the health and welfare of their supportive families. Military missions benefit when the Warfighters' families are healthy and well.	*Publications: 5* *Patent: 1* *Presentations: 5* *Funding obtained: 1 (R21 from NCI)* *Degrees obtained: 1 Ph.D. awarded* *Employment: 2*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Pediatric Brain Tumor				
CA101163 $117,975 Closed	Li/ 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 models to better understand carcinogenesis and its treatment. Created two orthotopic xenograft models for DPIG via the engrafting of autopsy tumor cells into the brains of SCID mice. Demonstrated that xenograft tumors could replicate key histopathological features of the original tumor. MR: Advancing genetic research has a direct application to active, reserve, and retired US 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.	*Publications: 1 (Nature Medicine)* *Presentations: 1* *Funding obtained: 5 (including 1 NIH R01)*
CA120318 $400,425 Pending Closeout	Huang/ 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: To study the functions of bone marrow-derived inflammatory cells (BMDCs) in the progression of pediatric glioma and develop therapeutic strategies to target a specific population of BMDCs to suppress the malignant transformation of gliomas. Identified a unique population that could potentially be used for glioma diagnosis and prognosis. Validated changes of myeloid and endothelial lineages during glioma progression and observed the increase of myeloid derived suppressor cells and endothelial progenitor cells in murine glioma models. MR: Military missions benefit when military families are healthy and well.	*Publications: 2* *Presentations: 2*
CA130562 $169,472.56 Closed (Early Termination)	Mulcahy Levy/ University of Colorado Denver	Targeting BRAF V600E and Autophagy in Pediatric Brain Tumors	RP: Found that inhibiting autophagy enhances the activity of BRAF inhibitors and may prevent acquired resistance to treatment in tumors. MR: The health and welfare of the force are partially determined by the health and welfare of their supportive families. Military missions benefit when the Warfighters' families are healthy and well.	*Presentations: 1* *Funding: 1 (NIH K08)*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Pediatric Cancer				
CA110045 $80,401.50 Closed (Early Termination)	Garcia/ University of North Carolina at 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. Found that Aspm becomes co-opted during medulloblastoma formation to support tumor growth by reducing stress to genomic DNA during cell division. Also, found that targeting Aspm can reduce medulloblastoma growth. MR: The health and welfare of the force are partially determined by the health and welfare of their supportive families. Military missions benefit when the Warfighters' families are healthy and well.	*None.* *Award terminated early because the PI received a second postdoctoral position at the BioDonostia Institute in San Sebastian*
CA110089 $381,600 Closed	Shi/ University of Texas 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. Results show that the chromatin remodeler Brg1 is required for medulloblastoma growth in primary culture and that its deletion inhibits progression. This indicates that the chromatin remodeling complex BAF, through Brg1, is a therapeutic target for Shh-type medulloblastoma. MR: The health and welfare of the force are partially determined by the health and welfare of their supportive families. Military missions benefit when the Warfighters' families are healthy and well.	*Publications: 4* *Presentations: 2* *Employment: 1 (PI was promoted from Postdoctoral Fellow to Instructor)*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Pediatric Cancer				
CA110407 $308,584 Closed	Jedlicka/ University of Colorado 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. Determined that the hypoxia response is mixed with both tumor promotional and tumor inhibitory effects in Ewing Sarcoma. A new, more specific, target downstream of HIF1α, KDM3A, has been identified and was established to be an important tumor and metastasis promoter in Ewing Sarcoma as well as a novel therapeutic target. MR: The health and welfare of the force are partially determined by the health and welfare of their supportive families. Military missions benefit when the Warfighters' families are healthy and well.	*Publications: 1* *Presentations: 1* *Funding obtained: 2 (R01 from NCI; Research Scholar Award from ACS)*