FISCAL YEAR 2017
REPORT TO CONGRESS

U.S. ARMY MEDICAL RESEARCH AND MATERIEL COMMAND

CONGRESSIONALLY DIRECTED MEDICAL RESEARCH PROGRAMS

PEER REVIEWED CANCER RESEARCH PROGRAM

August 2018

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Peer Reviewed Cancer Research Program
Fiscal Year 2017 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 114-263, page 194, and House Report 114-577, page 274, and the Public Law 115-31 FY17 Consolidated Appropriations with Explanatory Statement 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 FY12-FY17 PRCRP, research accomplishments, and the relevance of PRCRP-supported research to Service members and their families. Assistance agreements (awards) have a period of performance of 4 years or less. The FY12-FY17 update provides information on actively monitored awards by the CDMRP. Previous updates for FY09-FY16 can be accessed at http://cdmrp.army.mil/prcrp/reports/reports.

FY09-FY17 PEER REVIEWED CANCER RESEARCH PROGRAM BACKGROUND AND OVERVIEW

From its inception in FY09 through FY17, 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 while management and withhold costs are kept low. In FY17, 95% of the PRCRP appropriation went toward research and 5% toward management costs.

The overarching theme of the PRCRP is to improve the quality of life of those Service members, their families, and the American public affected by cancer. This singular idea emphasizes the PRCRP's strategy of funding research into cancers that may develop due to exposures relevant to unique military situations/settings and addressing knowledge gaps in cancer care and research that may have a profound effect on mission readiness and the health and well-being of all military beneficiaries. Through innovative mechanisms, militarily relevant focus areas, and targeted investment strategies to develop the next generation of cancer researchers, the PRCRP answers the need to promote high-impact research for cancer prevention, detection, treatment, and survivorship for Service members, their families, and the American public.

Table 1: PRCRP Appropriation and Topic Areas Per Fiscal Year

Fiscal Year	Public Law	Appropriation/ (Awards) ‡	Topic Areas*
2009	110-329	$16 million (M) (38)	$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
2010	111-118	$15M (30)	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
2011	112-10	$16M (44)	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
2012	112-74	$12.8M (27)	Melanoma and other skin cancers; Pediatric brain tumors; Genetic cancer; Pancreatic cancer; Kidney cancer; Blood cancer; Colorectal cancer; Mesothelioma; and *Listeria* vaccine for cancer
2013	113-6	$15M (27)	Melanoma and other skin cancers; Pediatric brain tumors; Genetic cancer; Pancreatic cancer; Kidney cancer; Blood cancer; Colorectal cancer; Mesothelioma; and Neuroblastoma
2014	113-76	$25M (47)	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
2015	113-235	$50M (110)	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
2016	114-113	$50M (89)	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
2017†	115-31	$60M (90)	Bladder cancer; Brain cancer; Cancer in children, adolescents, and young adults; Colorectal cancer; Immunotherapy; *Listeria*-based regimens for cancer; Liver cancer; Lymphoma; Melanoma and other skin cancers; Mesothelioma; Neuroblastoma; Pancreatic cancer; Pediatric brain tumor; Stomach cancer

*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.
†FY17 recommended awards under negotiation at the time of the writing of this report.
‡Number of awards represents all open, pending close-out, and closed awards; does not include withdrawals.

In FY17, the PRCRP funded 76 applications (representing 90 separate awards) of the 459 full applications received for a 17% funding rate. For more information on the award selection process, access the Principal Investigator Information Paper (http://cdmrp.army.mil/prcrp/pdf/W81XWH-17-PRCRP_InformationPaper.pdf). All FY17 awards initiated research by 1 October

2018. 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.

Over the years, PRCRP funded and managed numerous topic areas as directed by Congress. Applications are evaluated using a two-tier review system, including peer review (the assessment of the technical merit and impact) and programmatic review (the comparison of each application with the portfolio composition and intent of the published program announcement). Figure 1 shows the percentage of dollars invested in each topic area from FY12-FY17. In each fiscal year, many factors affect the investment portfolio, including whether or not a topic area has been included; the number of applications received 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. Each topic area is considered during the programmatic review to ensure a balanced portfolio with respect to the specific fiscal year topic areas. Table 2 shows total research recommended for funding, by topic area, for FY17.

Figure 1: FY12-FY17 PRCRP Research Investment Per Topic Area (% of Total Research Dollars)

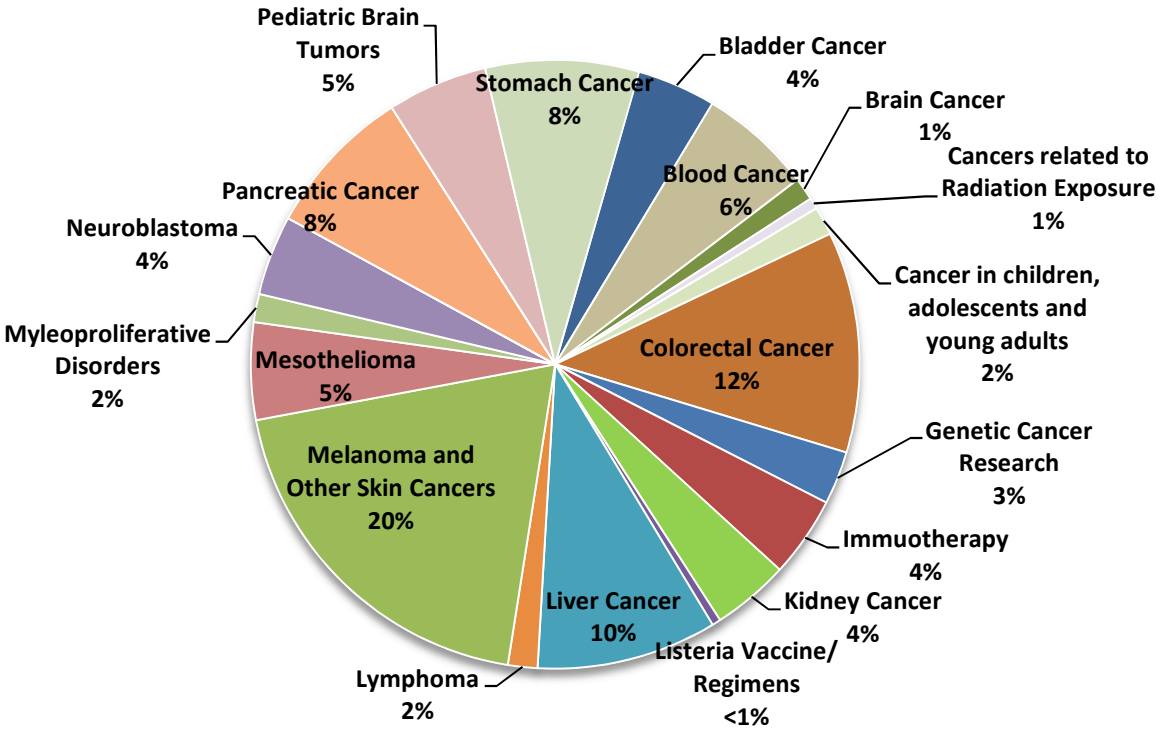

Table 2: Total Research Dollars Invested Per Topic Area for FY17

Topic Area	Total Dollars Recommended for Investment ($M)*
Bladder cancer	$2.8
Brain cancer	$2.8
Cancer in children, adolescents and young adults	$3.3
Colorectal cancer	$8.9
Immunotherapy	$2.5
***Listeria*-based regimens for cancer**	$0.56
Liver cancer	$5.0
Lymphoma	$2.8
Melanoma and other skin cancers	$10.3
Mesothelioma	$1.6
Neuroblastoma	$2.3
Pancreatic cancer	$4.0
Pediatric brain tumors	$4.2
Stomach cancer	$2.5
Total Research Investment	**$53.3**

*Amounts in the *Recommended for Investment* column include applications designated *Alternates* funded after publication of the Principal Investigator Information Paper (http://cdmrp.army.mil/prcrp/pdf/W81XWH-17-PRCRP_InformationPaper.pdf). FY17 recommended awards were under negotiation at the time of this writing and could change once negotiations are complete.

CANCER RESEARCH RELEVANCE: SERVICE MEMBERS AND THEIR FAMILIES

As a research funding program, the most significant method the PRCRP has to influence the quality of life of Service members and their families is to release impactful funding solicitations for research emphasizing the health and well-being of the military community. With input from active-duty oncologists on the Programmatic Panel, the PRCRP acknowledges three core issues/knowledge gaps with respect to Service members affected by cancer: the need for decreased toxicity of treatments, a decrease in the complexity of care, and the need to identify gaps in cancer surveillance. The FY17 PRCRP addressed these core issues and relevance to military service by ***requiring*** that all applications address at least one of the FY17 PRCRP Military Relevance Focus Areas, as shown in Table 3.

Table 3: FY17 Military Relevance Focus Areas

Environmental Exposures	Militarily relevant risk factors associated with cancer (e.g., ionizing radiation, chemicals, infectious agents, and environmental carcinogens)
Mission Readiness	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

Environmental Exposures

The PRCRP recognizes the hazards that members of the military may encounter. Service members, deployed across the world both in developed and developing nations, sustain environmental exposures linked to cancer risk. Multiple dangers have been identified that may play a role in the risk of carcinogenesis. 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, and ultraviolet radiation, among others (Table 4). The Department of Veterans Affairs (VA) has acknowledged that certain exposures increase the cancer risk of Service members and their families (Table 4).

Table 4: Cancer Risks and Mission Readiness

Topic Area	Military Gap	Relevance to Service Members, Their Families, and Veterans*
Bladder Cancer	Exposure	4th most common cancer in U.S. Veteran population; 2x incidence rate in Veteran population compared to general population linked pesticide containing arsenic
Adult and Pediatric Brain Cancer	Exposure/ Readiness	Adult Brain Cancer: Occupational exposure link (especially electromagnetic fields) Pediatric Brain Tumor (PBT)/Neuroblastoma: In all childhood populations, PBT has the highest mortality rates of any childhood cancer; affects mission readiness
Cancers in children, adolescents, young adults	Readiness	Active duty Service members' support system (family members) cancers affect mission readiness: 86% of the military are under the age of 39 (adolescents and young adults 15-39 years of age).
Gut Cancers (Colorectal, Liver, Pancreatic, Stomach Cancer)	Exposure/ Readiness	Colorectal Cancer: Active duty screening decreases the mortality rates, but report in 2008 showed only 58% up to date on screening; Infectious diseases may be implicated. Liver Cancer: Veteran population has an increased Hazard Ratio: Increased alcohol use leads to increased risk. Pancreatic Cancer: Direct link to environmental exposures (herbicides, smoking) may increase Odds Ratio in Veterans. Stomach Cancer: Due to increased exposure to infectious agents (*H. pylori*), Veterans may have an increased risk.
Lymphoma	Exposure	Exposure to toxic chemicals/herbicides shown to increase risk; VA acknowledged association of Agent Orange and other herbicides to certain cancers in Veterans.
Melanoma and other skin cancers	Exposure/ Readiness	Studies have shown an increase risk of developing melanoma when exposed to high intensity solar radiation (with respect to area of deployment): Increased risk compared to the Surveillance, Epidemiology and End Results (SEER) data.
Mesothelioma	Exposure	Veterans account for >33% of all cases in the U.S.: Exposure to asbestos leading cause.

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

Mission Readiness

Exposures are not the only cancer risk factors to Service members, their families, and other beneficiaries. The core issues identified affecting Service members and their families (the need for decreased toxicity of treatments, a decrease in the complexity of care, and the need to identify gaps in cancer surveillance) are addressed by the PRCRP through the second PRCRP Military Relevance Focus Area (Table 3) gaps within the cancer care spectrum. The cancer care spectrum covers research in biology/etiology, prevention, detection/diagnosis, prognosis, treatment, and 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, decreasing mission readiness. This extends to Service members' families. When a family member is in treatment for or receives a diagnosis of cancer, the 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 disruption of a unit's mission readiness. For more information on research accomplishments of the PRCRP from FY09-FY16, refer to http://cdmrp.army.mil/prcrp.

There are more than 300,000 military beneficiaries with a cancer diagnosis, for a prevalence of 4.1%, comprised of more than 60 different cancer types. In FY02, the cost of cancer care within the Military Health System (MHS) was over $1 billion.[1] The MHS continues to diagnose and treat active duty Service members for a wide variety of cancers.[2] Addressing the key elements of cancer research and patient care is crucial to the mission of the PRCRP in relation to Service members, their families, Veterans, and the American public. The PRCRP funds underrepresented and underfunded cancers[3] for the health and welfare of the designated population. Investment in basic research lays the foundation for long-term applied and translational research while funding more applied areas shifts the field toward the ultimate goals, advancing mission readiness while increasing quality of life for those affected by cancer. The impact of research funding in the area of cancer with respect to the military will reduce the burden of cancer on military families and improve force readiness. Furthermore, successful new studies will lead to preventatives that are more effective, diagnosis/detection methods, prognostic information, new treatments, and better ways to cope with quality of life issues.

SUMMARY OF RELEVANCE AND PROGRESS OF PRCRP AWARDS

Table 5 includes a summary of open FY12-FY17 awards as of 30 June 2017. In accordance with the congressional language,* this report includes the log number, topic area, last name of Principal Investigator (PI), award amount, institution, title, research progress, and military relevance for each award funded. Closed awards may be reviewed in Appendix A. For older awards (FY09-FY11), refer to the PRCRP website (http://cdmrp.army.mil/prcrp) to review previous PRCRP Reports to Congress and the CDMRP Search Awards site (http://cdmrp.army.mil/search.aspx).

*"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."

Table 5: Research Progress and Military Relevance of Under Negotiation, 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 (BC)				
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 most curable. Furthermore, if the VA determines AO is a risk factor for BC, those exposed may have additional compensation and/or service-connected disability benefits.	*New Research – no outcomes reported to date*
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 by mutating single-stranded DNA, inducing genomic instability and mutations that fuel the evolution of chemotherapy-resistant clones. MR: Within the Department of Veterans Affairs (VA) population, urothelial cancer is the fourth most common cancer. Urothelial cancer is also associated with several risk factors that are relatively common in the Veteran and active Service member populations such as smoking and exposure to agent blue and industrial solvents (Institute of Medicine, 2014).	*New Research – no outcomes reported to date*

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 U.S. 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.	*New Research – no outcomes reported to date*
CA160312/P1/P2 $1,680,259 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 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.	*New Research – no outcomes reported to date*

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) PDT and thus greatly improves therapeutic efficacy with minimal collateral damage in the bladder. MR: Bladder cancer is the fourth most common cancer in U.S. Veterans due to several exposure risks: higher prevalence of smoking than in civilian population, exposure to Agent Orange in Vietnam, and increased exposure to other industrial solvents like benzene.	*New Research – no outcomes reported to date*
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 military 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 and their families.	*New Research – no outcomes reported to date*
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. MR: Tobacco smoking is the most common etiology for bladder cancer, and military Veterans have a higher incidence of smoking and developing smoking-related cancers. The second most common bladder cancer etiology is environmental carcinogens and military personnel are at much higher risk for exposure to bladder carcinogens.	*New Research – no outcomes reported to date*

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 (1) study the S phase-specific roles of the Mre11 complex (typically associated with DNA damage response) and how mutations observed in bladder cancer influence these roles and (2) 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 in 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.	*New Research – no outcomes reported to date*
CA170270/P1/P2 $871,967 Under Neg	Meeks/ Northwestern University Svatek/ University of Texas Health Science Center at San Antonio McConkey/ Johns Hopkins University	Investigation of Genetic and Immune Mechanisms of Response to BCG for Non-Muscle Invasive Bladder Cancer: A Translational Study of S1602	RP: The goal of this project is to identify both the tumor-specific and immune-mediated responses that contribute to the tumoricidal effect of Bacillus Calmette-Guerin (BCG), leveraging samples collected from the Southwest Oncology Group 1602 (S1602) that included over 900 patients treated with BCG. MR: Bladder cancer is the fourth most common cancer among Veterans and develops secondary to smoking and exposure to environmental and deployment-related carcinogens. The successful completion of this project will have profound impact on the health and well-being of active duty Service members, Veterans, and their beneficiaries.	*Research not yet initiated*
CA170373 $615,076 Under Neg	McGrath/ University of Rochester	Nanomembrane Capture and Characterization of Cancer-Derived Exosomes in Urine	RP: The PI will optimize methodology to efficiently capture exosomes (>50% captured) from human urine samples and demonstrate the ability to distinguish exosomes derived from uroepithelial carcinoma from those that are not. MR: Recent findings have linked Agent Orange exposure to a statistically higher incidence of bladder cancer. The herbicide was used liberally to destroy jungle canopies in the Vietnam war and forests in the demilitarized zone during the Korean war.	*Research not yet initiated*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
BLADDER CANCER				
CA170470 $608,000 Under Neg	Lokeshwar/ Georgia Regents University	Development of Novel Noninvasive Tests for Prognostic Predictions for Bladder Cancer	RP: The main objectives of this proposal are to evaluate the efficacy of novel urine tests to (a) detect bladder cancer recurrence and early detection of muscle invasive bladder cancer, and (b) predict whether a patient will respond to Gemcitabine plus cisplatin neoadjuvant chemotherapy. MR: Smoking and chemical exposure are the major risk factors for bladder cancer. Compared to the general population, Veterans and active duty Service members are twice as likely to be active or previous smokers. Additionally, recent evidence suggests a link between Agent Orange exposure and bladder cancer.	*Research not yet initiated*
BLOOD CANCERS				
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.	*Publication: 1*
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.	*None 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 to Agent Orange increased the incidence rate of MM. This project could improve the therapeutic efficacy to MM and benefit the military population.	*Publication: 1* *Patent application: 1* *Presentation: 1*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
BLOOD CANCERS				
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 and their families. This work will provide an understanding of the mechanism between obesity and cancer, which could benefit the military population in the long term.	*Funding Obtained: 1* *Miscellaneous: 1* *Presentation: 4*
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 the potential to develop HIV/KSHV-related malignancies. PEL is a form of AIDS-related blood cancer.	*Publications: 15* *Funding Obtained: 2* *Presentations: 5*
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.	*None to date*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
BLOOD CANCERS				
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 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.	*Publications: 2* *Presentations: 4*
BRAIN CANCER				
CA170278 $602,000 Under Neg	Noushmehr/ Henry Ford Health System	Epigenomic Master Regulators that Define IDH1/2 Mutant Glioma Tumor Progression	RP: The PI hypothesizes that G-CIMP-high tumors relapse as G-CIMP-low gliomas due to variations in DNA methylation and other epigenomic events, which then drive glioma progression. He will use next-generation sequencing and insights into the relationship between transcription factor, histone modifications, and DNA to investigate the functional genomic elements that define brain cancer progression between G-CIMP-high and G-CIMP-low. MR: Although environmental risk factors for glioma and glioblastoma remain poorly defined, with the exception of exposure to ionizing radiation, evidence has shown that traumatic brain injury may predispose Service members to gliomagenesis via inflammation and stem cell transformation.	*Research not yet initiated*
CA170769 $508,129 Under Neg	Warram/ University of Alabama at Birmingham	Dual PET/Fluorescence Imaging of Glioma with an MMP-14-Activatable Peptide Probe	RP: The PI will validate the concept of a matrix metalloproteinase 14 activatable probe for PET/NIRF imaging of glioblastoma multiforme (GBM) and build the foundation to enable probe-guided resection of GBM in preclinical animal models, toxicology assessments, and, in future studies, trials in patients with GBM. MR: Exposure to ionizing radiation is the main external risk factor associated with GBM. Individuals including military personnel exposed to nuclear weapons testing or other types of ionizing radiation have increased risk compared to the general population of developing GBM.	*Research not yet initiated*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
BRAIN CANCER				
CA170948 $624,000 Under Neg	Van Meir/ Emory University	Role of N-Cadherin in the Therapeutic Resistance of Glioblastoma	RP: The PI will test the hypothesis that N-cadherin-mediated cell-cell adhesion induces adaptive resistance to radiotherapy in glioblastoma multiforme (GBM) by suppressing Wnt/β-cat signaling in glio stem-like cells, resulting in a state of slow proliferation and stemness properties. Furthermore, he will test that therapeutic targeting of this process will prevent or reduce cancer cell resistance and augment patient survival. MR: If these studies support the use of N-cad pathway inhibitors as therapeutic radiosensitizers, these agents could be rapidly translated in GBM patients as they are already approved for clinical trials. Success of this project will lead to the development of better therapies for the treatment of military personnel, their dependents, retirees, Veterans, and the American public afflicted with GBM.	*Research not yet initiated*
CA171074 $577,200 Under Neg	Tiwari/ Case Western Reserve University	Systems Biology Approach to Predicting and Assessing Response to Chemoradiation for Brain Tumors	RP: The objectives of the proposed study are to develop and validate predictive EBI features for (a) identifying non-responders to chemoradiation therapy on pre-treatment MRI, and (b) distinguishing radiation necrosis from tumor recurrence on post-treatment MRI. MR: Brain tumor is a frequently occurring cancer in the Veteran population; over 40% will develop a suspicious post-treatment lesion within a year after chemoradiation therapy. These patients could benefit from the clinically actionable tools developed in this project. Additionally, this proposal involves a collaboration with the Cleveland VA for independent validation of the tools. After successful validation of these tools, they will be embedded into the VA network to directly impact treatment management in brain tumors.	*Research not yet initiated*
CA171145 $527,162 Under Neg	Leavenworth/ University of Alabama at Birmingham	Boosting the Systemic and In Situ CD4+ T-Cell Responses to Malignant Glioma by Oncolytic HSV Virotherapy	RP: The goal of this project is to dissect the mechanisms of the antiglioma immune response that occurs as a result of treatment with the oncolytic virus, IL-12-oHSV. MR: Effective therapies represent unmet clinical needs for malignant glioma patients, including Gulf War Veterans, who are vulnerable to brain cancers. Results from the proposed study may form the foundation of future clinical approaches that benefit both the military personnel and the general population.	*Research not yet initiated*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
CANCER IN CHILDREN, ADOLESCENTS, AND YOUNG ADULTS				
CA170146 $622,000 Under Neg	Jedlicka/ University of Colorado at Denver	Identification of Novel Epigenetic Modifiers of Metastasis Progression in Ewing Sarcoma	RP: A project employing an in vivo genomic screen to identify modifiers of the epigenome that are necessary for metastasis of Ewing Sarcoma. MR: Ewing Sarcoma is an aggressive cancer of bones and soft tissues that disproportionately affects individuals within the age range eligible for active military service.	*Research not yet initiated*
CA170218 $616,000 Under Neg	Modiano/ University of Minnesota Twin Cities	Mechanisms of Resistance to Immunotherapy in Osteosarcoma	RP: A study to describe the relationship between CD28, a receptor located on T cells, and resistance to immune checkpoint blockade in osteosarcoma mouse models. The PI will investigate the mechanisms by which microRNAs targeted to CD28 are released from osteosarcoma-derived exosomes as a way for the cancer to evade host immune response. MR: Osteosarcoma, a cancer that primarily affects children, adolescents and young adults, has a slightly higher prevalence in military families than the general population likely due to the fact that 86% of active Service men and women fall within the adolescent and young adult age bracket.	*Research not yet initiated*
CA170273 $732,000 Under Neg	Sykes/ Institute for Cancer Research	Targeting the Unfolded Protein Response in Pediatric Leukemia	RP: This study is to identify the transcriptional targets of ATF4 and XBP1S and assess chemical inhibitors in MLL-rearranged acute myeloid leukemia (AML). MR: Service members are at higher risk for leukemia due to the exposure of chemicals and radiation. This study could potentially bring new therapeutics for AML	*Research not yet initiated*
CA170549 $641,000 Open	Kirsch/ Duke University	Modeling the Impact of Radiation Protectors on Radiation-Induced Sarcoma Risk	RP: This project aims to understand how sarcoma (cancer of muscles and connective tissue) develops following radiation exposure. The investigator believes that p53, a protein that protects cells from cancer, plays an important role. The study will use mice that do/do not express p53, exposing them to radiation and following the development of tumors. The study will provide insight into how radiation drives carcinogenesis. MR: Sarcoma is one of the most common childhood cancers. One major risk factor for developing sarcoma is exposure to radiation, either from radiotherapy for a different cancer type, or a radiological disaster like the Fukashima power plant meltdown in 2011.	*Research not yet initiated*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
CANCER IN CHILDREN, ADOLESCENTS, AND YOUNG ADULTS				
CA171025 $662,124 Open	Halene/ Yale University	Mechanisms of Bone Marrow Failure and Leukemia Progression in Primary Human Fanconi Anemia Stem Cells in a Novel FA PDX Model	RP: This study is to identify the causes and underlying mechanisms of oncogenesis in Fanconi Anemia (FA) using an FA PDX model MR: Military beneficiaries are at higher risk to develop leukemia and cancer due to exposure to radiation and chemicals specifically related to war that may adversely interact with FA pathway mutations	*Research not yet initiated*
CANCERS RELATED TO RADIATION EXPOSURE				
CA140307 $475,959 Open	Chao/ Duke University	A Novel Therapeutic Target for Radiation-Induced Hematological Malignancies: Calcium Calmodulin Kinase 2	RP: The PI determined that the kinase CaMKK2 plays an important role in the initiation and progression of lymphoma and myeloma and that inhibition of this kinase blocks tumor-induced myeloid cell-mediated immune suppression and activates an antitumor response. 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 submitted two provisional patent applications: (1) for using CaMKK2 blockers as immune-modulators of the tumor microenvironment, and (2) for using CaMKK2 blockers as medical countermeasures for hematopoietic acute radiation syndrome. MR: Veterans who participated in activities with radiation exposure have a higher risk of developing blood cancer as they age; few drugs are approved to mitigate the radiation injury.	*Patents: 2* *Publications: 2* *Presentation: 1*
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: To date, Dr. Natarajan has 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. He also developed mouse models that will be used for future studies on the acute and delayed effects of radiation-induced development of cancer. 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*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
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 2D cell cultures and will test the activity of these compound combinations in 3D cell culture as well as in vivo PDX models. The PI is also developing an assay suitable for high-throughput screening that utilizes 3D cell culture, which may better identify lead compounds with antitumor activity against CRC cells. . MR: CRC is the second leading cause of cancer death in the U.S., 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. The PI has confirmed that genetic ablation of TMEM9 in vivo is protective against tumorigenesis. In the coming year, the PI will investigate the utility of pharmacological regulation of TMEM9 in tumor prevention. MR: U.S. military 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.	*Presentation: 1* *Funding Obtained: 1* *Publications: 3*
CA140577 $310,000 POP EXP	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: To quantify the relationship between 25-hydroxyvitamin 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*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
COLORECTAL CANCER (CRC)				
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 has completed as has optimization of DNA methylation marker analysis. Association analysis will occur in the third year of this project. 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.	*None to date*
CA140772 $466,500 Open	Messersmith/ University of Colorado at Denver	Targeting the ALDH+ Tumorigenic Population in Colorectal Cancer	RP: This study aims to identify new combination therapies that are effective against the small population of cancer stem cells believed to medicate chemotherapeutic resistance in CRC patients. By isolating tumor-initiating cells from patient-derived xenografts, the PI has performed a compound screen to identify compound combinations that work synergistically with inhibitors of the WNT signaling pathway. The PI has identified new therapeutic combinations that are more effective at inhibiting cancer stem cell growth than the monotherapy. Validation of these combinations is underway. MR: CRC is the second leading cause of cancer death in the U.S.. 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 to date*

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. She has also shown that these particles can target and selectively kill tumor cells in vitro. Work continues on optimizing these nanoparticles for targeted delivery to cancer site in vivo. 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 quality of life.	*Presentations: 2* *Patent: 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 that were predicted to perturb pathways with known importance in CRC 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: 8* *Presentations: 2*

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 CRC risk. The PI has found that mice devoid of B7-H1 expression have a higher incidence of colon cancer, more severe colitis, and blunted INFγ signaling when compared to wildtype mice. In the coming 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 military healthcare 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 to date*
CA150370/P1/P2 $1,117,600 Open	Yeung; Pillarisetty/ University of Washington Tian/ Institute for Systems Biology	Tumor Slice Culture: A New Avatar in Personalized Oncology	RP: To establish a tissue-based 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. In the first year of the award, the research team has begun to collect patient samples from the associated clinical trial and initiate sensitivity assays on a small cohort. The utility of this technique will be examined in the future years of this project once an appropriate number of patients have been recruited. 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.	*None 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%.	*Presentations: 2* *Funding Obtained: 1 (Pending)*
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 PI has had some success with the development of siRNA-conjugated gold particles. The utility of the AuNPs will be assessed in vivo for a mouse model of CRC in the second year of the award. 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 disease (irritable bowel disease, Crohn's disease, and CRC) later in life.	*None 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. In the first year, the PI utilized radiology and pathology data to spatially map post-treatment changes in CRC patients. Initial results also indicate that noninvasive MRI data can be used to predict cancer phenotypes previously only determined by biopsy and/or resection. These characteristics include cancer stage, KRAS status, and response to treatment. Validation on larger patient cohorts from university hospitals as well as the Cleveland VA Medical Center will be performed in the coming years to determine the utility of these noninvasive prediction methods. 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.	*Publications: 7* *Patent: 1* *Presentations: 6* *Website: 1*
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. Initial results support the idea that different p53 mutations contribute to 5-FU resistance in unique ways and that DPYD expression can either support resistance or sensitivity to 5-FU depending on the specific p53 mutation . MR: CRC is also the third most frequently occurring cancer in the military population, occurring in up to 8% of Veterans and 5% of active duty personnel.	*Presentation: 1* *Miscellaneous: 1*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
COLORECTAL CANCER (CRC)				
CA150808 $125,250 POP EXP	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 has investigated the differences in survival, tumor incidence/location, and histopathology of MMR-impaired mice and shown that these tumors more closely mimic the disease phenotypes observed in human patients. Additionally, Msh2/TgfBRIIhu double mutant mice have reduced colon cancer survival. The PI plans to further examine the impact microbiota alteration has on tumorigenesis 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.	*None to date*
CA150899 $113,625 POP EXP	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. In vivo experiments using an LXR blocking agent shows CRC tumor growth inhibition. This antitumor effect requires an intact immune system, suggesting that this compound is not acting directly on the tumor but instead boosting the immune recognition and clearance of these cells. 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.	*Presentation: 1*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
COLORECTAL CANCER (CRC)				
CA150908 $108,867 Open	Gomez/ University of Kansas Center for Research, Inc.	A Role for APC in Goblet Cell Function and the Unfolded Protein Response	RP: A project to determine the regulation, role, and function of the tumor suppressor Adenomatous Polyposis Coli (APC) in unfolded protein response (UPR) within colon cancer cells. The PI has observed colitis-induced patterning of both the APC protein and a marker of UPR within the colons of mice with chemically induced colitis. The second year of the award will further characterize these changes in human colitis tissue as well as other mouse models. 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.	*None to date*
CA160344/P1 $802,575 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. 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.	*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)				
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 noninvasive techniques. 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.	*New research – no outcomes reported to date*
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 CRC cell lines. Kif18A is a motor protein associated with increased CRC metastasis and poor prognosis. MR: Statistics show that CRC is the second most deadly cancer for Service members.	*New research – no outcomes reported to date*
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. MR: Frequent exposure to cancer-associated agents places the U.S. military population at higher risk for CRC.	*New research – no outcomes reported to date*
CA170223/P1/P2 $834,029 Under Neg	Waldman/ Thomas Jefferson University Weinberg/ Institute for Cancer Research Dominitz/ Seattle Institute for Biomedical and Clinical Research	Oral GUCY2C Ligand Blocks Colorectal Tumor Progression in Patients	RP: A project to determine whether treatment with the drug linaclotide, to restore tumor suppressor GUCY2C signaling in CRC patients, can repair the epithelial dysfunction observed in patients with adenomas or carcinomas. The research team will then use tissue collected from these patients to more precisely describe the mechanism of action of this drug. MR: The impact of prevention strategies for CRC on the military health system can best be appreciated by considering that in 2015 medical care for new cases of CRC will cost the VA Health System ~$400M annually, while the economic impact of each year of life lost is ~$170M annually.	*Research not yet initiated*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
COLORECTAL CANCER (CRC)				
CA170468 $616,877 Under Neg	Linden/ Mayo Clinic and Foundation, Rochester	Feedforward Signaling Between Glia, Neurons, and Mast Cells Contributes to Polyp Formation and Growth	RP: A project to determine signal mechanisms that contribute to increased innervation within the tumor microenvironment. The PI will examine the in vivo contribution of glia, neurons to polyp development and growth in mouse models of CRC. MR: This project has the potential to contribute to better understanding of the linkage between CNS dysfunction and oncogenesis, a major knowledge gap in the field of CRC.	*Research not yet initiated*
CA170613 $616,000 Under Neg	Wong/ Oregon Health & Science University	Development of a Novel Circulating Tumor Cell Population for Early Detection of Recurrent Colorectal Cancer	RP: To investigate the function and relevance of circulating hybrid cells (CHCs), a fusion of macrophages and cancer cells, in colon cancer. Aims to determine if CHCs can be a biomarker to track therapeutic response and disease in colon cancer patients. CHCs from colon cancer patients will be analyzed for gene expression profiles. Then the CHCs will be studied pre- and post-treatment to determine if treatment alters this population of cells and whether detection of the cells predict response to treatment. MR: Colon cancer is one of the most common cancers, which will inevitably impact Service members, Veterans, and their families.	*Research not yet initiated*
CA170670 $596,450 Under Neg	Brock/ University of Texas at Austin	Targeting Resistance in Colorectal Cancer with a Novel Lineage-Tracking Technology	RP: To validate a novel fluorescent "DNA barcoding" method called BAASE that can track heterogeneous cell populations. CRC cells will be tracked over time using BAASE to validate its efficiency in isolating specific populations. Then, these cells will be treated with chemotherapeutics and monitored to understand how drugs change the populations over time. Cells resistant to chemotherapy will be isolated for further characterization and tested for response to other drugs. MR: Chemoresistance is a major issue in the treatment of many cancers, including colon cancer. This award addresses gaps in cancer prognosis and treatment, which impacts Service members, Veterans, and their families.	*Research not yet initiated*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
COLORECTAL CANCER (CRC)				
CA170751 $634,000 Under Neg	Gamero/ Temple University	The Role of the Gut Microbiome in Colorectal Cancer	RP: A project to understand the genetic factors involved in shaping the intestinal microbial composition. The PI will investigate whether the microbiome of Stat2-deficient mice can be protective against both colitis and CRC. MR: Military personnel based in the U.S. or deployed abroad are exposed to a multitude of risk factors that include environmental, genetic, and changes in diet, and are pathogenic in nature, that may cause intestinal inflammation and changes to the structure of the gut microbiota.	*Research not yet initiated*
CA170922 $526,001 Under Neg	Chen/ University of Michigan, Ann Arbor	Role of Noncoding Small RNAs in Colorectal Cancer Progression	RP: A project to investigate whether small non-coding RNA fragments are predictive of colon cancer development and whether they impart an immune modulatory effect to promote tumor growth and maintenance. MR: With current CRC therapies, overall survival of patients has been extended on average only two years while remaining the third leading cause of cancer-related mortality.	*Research not yet initiated*
CA171000 $658,800 Open	Arora/ Institute for Cancer Research	Developing Biomarkers of Response to Chemoradiation Therapy in Rectal Carcinoma: Toward Precision Medicine	RP: A project to identify biomarker signatures for CRC patients who respond well to the current standard of care, neoadjuvant radiation therapy. The PI will compare both DNA and protein profiles of DNA damage, recognition, and repair pathways between patients with differing response to therapy to develop a dual component signature for therapeutic response prediction. MR: CRC incidence is increasing among young adults, a group of particular interest to the military.	*Research not yet initiated*
CA171019 $601,200 Open	Kelly/ Albert Einstein College of Medicine of Yeshiva University	Preventing Adverse Patient Responses to Cancer Chemotherapeutics	RP: A project to determine how the gut microbiome influences drug metabolism and contributes to adverse events in patients. The PI will attempt to correlate different metabolites of the anti-CRC drug CPT-11 to adverse events in patients and examine which components of the gut microbiome are responsible for their generation. MR: CRC is a common cancer among active duty military personnel and is the second leading cause of cancer-related deaths in the United States	*Research not yet initiated*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
COLORECTAL CANCER (CRC)				
CA171038 $626,832 Under Neg	Ellis/ The University of Texas MD Anderson Cancer Center	Paracrine Role of Endothelial Cells in HER3-Mediated Colon Cancer Cell Survival	RP: A project to identify the soluble factors secreted by liver endothelial cells that promote CRC survival MR: Even though there are 10 FDA-approved drugs for treating patients with metastatic CRC (mCRC), median survival of patients with mCRC is only ~2.5 years.	*Research not yet initiated*
CA171059 $615,240 Under Neg	LaBarbera/ University of Colorado at Denver	Reversing EMT as a Strategy to Identify Effective Drug Combinations for Metastatic Colon Cancer	RP: A project to evaluate the antitumor potential of new combination therapies targeting epithelial-mesenchymal transition in CRC using in vitro and in vivo techniques. MR: CRC is the third most prevalent type of cancer diagnosed with the second highest mortality rate, worldwide.	*Research not yet initiated*
CA171086 $623,668 Under Neg	Shah/ University of Michigan, Ann Arbor	The Role of NF-kappa B2 Pathway in Colon Cancer	RP: This project will further define the role of NF-κB2 signaling in cancer cell proliferation and the maintenance of a pro-tumorigenic microenvironment. The PI will measure the recruitment and function of immune cells within the tumor microenvironment of NF-κB2 deficient mice and patient-derived colon tumors. MR: Colon cancer is one of the most common cancers among active military personnel and standard therapies are not beneficial for over 40% of the patients at time of diagnosis.	*Research not yet initiated*
CA171098 $636,000 Under Neg	Hu/ Rutgers University	Chronic Stress and Its Effect on Cancer Therapy: Mechanism and Intervention	RP: This project aims to describe the signaling pathways involved in stress-induced chemoresistance in mouse models of CRC. The PI will then examine whether targeting these pathways can enhance chemosensitivity in these same models. MR: This project investigates the effect of chronic stress on therapeutic response in CRC.	*Research not yet initiated*
CA171136 $618,120 Open	Ganesh/ Memorial Sloan Kettering Cancer Center	Investigating L1CAM-Dependent Stem Cell Regeneration in Colorectal Cancer Metastasis	RP: A project to better understand the mechanisms required for CRC tumor initiation and metastasis. The PI will focus on proteins involved in maintaining intestinal epithelial integrity and examine in vitro and in vivo how disruption of cell-to-cell connections supports metastasis of CRC tumors. MR: CRC patients younger than 55 are 58% more likely to be diagnosed with metastatic disease, which is usually incurable.	*Research not yet initiated*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
COLORECTAL CANCER (CRC)				
CA171171 $545,040 Under Neg	Lowe/ Texas Tech University Health Sciences Center, Lubbock	Immunotherapeutic Targeting of Colon Cancer Vascularization to Achieve Long-Term Immunity Against Primary and Metastatic Disease	RP: A project to investigate and characterize a new therapeutic vaccine strategy against CRC. The PI will examine the acute therapeutic effect of these vaccines in tumor-bearing mice and examine whether immunity is maintained long-term in treated mice. MR: CRC is the third most common diagnosed cancer in the United States, and afflicting the specific age groups of active military personnel.	*Research not yet initiated*
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: The goal is to understand the 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: 3* *Funding Obtained: 2* *Funding Applied for: 2*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
GENETIC CANCER				
CA140303 $569,841 Open	Moldovan/ Pennsylvania State University	The PCNA-PARI Pathway of Genome Stability in Cancer	RP: PI demonstrated that human p53-deficient myeloid leukemia cells activate p21 expression and myeloid differentiation in response to damage. His work identified the signaling mechanism controlling myeloid leukemia differentiation as being NFκB, rather than p53, an unexpected finding. These findings significantly amplify the repertoire of known NFκB functions. Moreover, these studies show that p53-deficient cells can still respond to DNA damage via a p53-independent p21 regulatory mechanism, which may be conserved in other p21-dependent biological processes. 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.	*Presentations: 3* *Publications: 2*
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 pathway leads to a selective advantage for cells within the bone marrow that are predisposed to genomic instability upon low-level ionizing radiation. Mice deficient in specific DNA damage response 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.	*None to date*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
GENETIC CANCER				
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.	*None to date*
CA150795 $128,550 POP EXP	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 the 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; researchers do not have a complete understanding of initiation and progression of these diseases. 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.	*None to date*
CA150827 $108,350 POP EXP	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.	*None 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.	*Presentations: 2*
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. 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 duty military member with time commitments away from home.	*New research – no outcomes reported to date*
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. MR: Developing new CAR-T cell therapy to treat metastatic CRC will potentially benefit military beneficiaries as CRC incidence rate is skewed toward current Veterans due to age and exposure-related risks.	*New research – no outcomes reported to date*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
IMMUNOTHERAPY				
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. Using data from The Cancer Genome Atlas (TCGA), the investigator has identified multiple pathways that may mediate immunosuppression. The PI will also 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. 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.	*Publication: 1*
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 CAR-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. MR: The major cause of MM is chronic exposure to asbestos, which was a common occurrence in U.S. 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.	*New research – no outcomes reported to date*
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. 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.	*New research – no outcomes reported to date*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
IMMUNOTHERAPY				
CA160461/P1/P2 $1,241,250 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 rate, high morbidity, and protracted course has a disproportionate effect on parents, including those in the military.	*New research – no outcomes reported to date*
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. 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 U.S. military population than in the general population, according to the Automated Central Tumor Registry published by DoD.	*New research – no outcomes reported to date*
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 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.	*New research – no outcomes reported to date*

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. 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.	*New research – no outcomes reported to date*
CA160714/P1/P2 $1,052,800 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. 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.	*New research – no outcomes reported to date*
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.	*New research – no outcomes reported to date*

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.	*New research – no outcomes reported to date*
CA170734 $634,000 Under Neg	Lim/ University of California, San Francisco	Engineering Next-Generation CAR T Cells to Treat Pediatric AML: Enhancing Safety Through Dynamic Control and Specificity	RP: To develop next-generation immunotherapy with enhanced specificity and reduced toxicity to treat AML. MR: Military personnel and their children are at risk of developing clonal myeloid disorders due to the potential exposures to radiation or chemical mutagens.	*Research not yet initiated*
CA171008 $640,000 Under Neg	Reshef/ Columbia University Medical Center	Identification of Effector and Suppressive T-Cell Clones in Graft-vs-Host Disease	RP: To identify alloreactive T-cell clones in GvHD affected tissues and determine their individual function. MR: Blood cancers are more prevalent in young adults and in children of Service members. Allogeneic SCT is standard therapy in blood cancers and is performed in approximately 30,000 people worldwide each year, including many military personnel.	*Research not yet initiated*
CA171068 $642,500 Under Neg	Sarantopoulos/ Duke University	Breaking B-Cell Tolerance to Produce Antibodies that Eradicate Leukemias and Lymphomas	RP: To develop B-cell immunotherapies for the treatment of hematolymphoid malignancies. MR: Blood cancers, including lymphoma and multiple myeloma, are associated with exposure to chemical and biological agents from the Vietnam and Gulf Wars.	*Research not yet initiated*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
KIDNEY CANCER				
CA171157 $543,766 Under Neg	DeKosky/ University of Kansas Center for Research, Inc.	High-Throughput TCR Repertoire-Based Platforms for Antigen-Specific Cancer Immunotherapy	RP: To develop new systems for rapid, personalized, and antigen-specific T-cell receptor (TCR)-based immunotherapy that involve the isolation and re-delivery of tumor-specific TCRs to cancer patients. MR: Military populations show enhanced risk of several cancer types due to service-related exposure. Immunotherapy has an outsized benefit to the care and treatment of military Service members by the immune system's targeting of neoantigens generated by such exposures.	*Research not yet initiated*
CA120297 $364,353 POP EXP	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 (RCC). 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 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*
CA140497 $585,000 POP EXP	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 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: 3*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
KIDNEY CANCER				
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*
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.	*Publications: 2*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
KIDNEY CANCER				
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 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.	*None to date*
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.	*New research – no outcomes reported to date*
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*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
KIDNEY CANCER				
CA160728/P1/P2 $686,909 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 RCC samples collected from multiple trials, including one VA trial, to assess: (1) whether certain chromatin remodeling mutations ultimately influence 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.	*New research – no outcomes reported to date*
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. MR: 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 years old), and these patients present with advanced disease, which is more likely to recur.	*New research – no outcomes reported to date*
CA171143 $564,498 Under Neg	Sheridan/ Stony Brook University	Using Oral Delivery of Listeria-Based Cancer Vaccines to Target Gastrointestinal Cancers	RP: A project to test the utility of a new orally delivered listeria-based vaccine. The efficacy of the oral vaccine will be compared to intravenous immunization in mouse models of CRC. MR: Gastrointestinal cancers are the third most common cancers among VA patient populations.	*Research not yet initiated*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
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, an FDA-approved cancer treatment. Lead targets for combination therapy with palbaciclib were identified and validation of their synergistic anti-tumor effect is underway. MR: The incidence of hepatocellular carcinoma (HCC) is increasing in the United States, especially within the U.S. 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 overrepresented within the U.S. military and Veterans communities.	*None to date*
CA150245/P1/ P2/P3/P4 $1,411,884 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 HCC at different disease stages. Patient-derived xenografts from more than 100 HCC cases have been collected. In Year 2 of this award, 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 U.S. Veterans.	*None 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. The PI is working to establish the contribution of TSPY and other Y chromosome-expressed genes to liver cancer pathology. Overexpression of TSPY seems to support a pro-proliferation phenotype in HCC cells while another Y chromosome-expressed gene RBMY shows a bimodal effect. 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.	*Presentations: 2*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
LIVER CANCER				
CA150262 $437,152 Open	Albrecht/ VA Medical Center Minneapolis, MN	The Role of CDK2 in Hepatocellular Carcinoma	RP: Explores the mechanisms by which cell cycle regulator cdk2 contributes to HCC. The PI has confirmed that loss of CDK2 expression is highly protective against HCC development and in the next year of the award will identify genes contributing to cdk2-induced pathology. MR: The proposed research is highly relevant to military Veterans because of the increasing incidence of HCC in this population.	*None to date*
CA150272/P1/ P2/P3/P4 $1,628,557 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 resistance to sorafenib and other HCC therapies. 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 U.S., 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 overrepresented in the U.S. military and Veterans communities.	*None 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-HCV clearance. A cell-based model will be used to describe molecular changes that occur at the transcriptomic, epigenomic, and secretomic levels as a result of oncogenic HCV infection. MR: The prevalence of HCV infection in U.S. Veterans is more than threefold higher than in the U.S. general population. The number of Veterans with HCV-related liver cancer has increased ninefold over the past decade.	*Presentation: 1* *Publications: 11*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
LIVER CANCER				
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. In the first year of the award, the PI established that Angpt1 inhibition enhances the PD-1/PD-L1/2 inhibitor-mediated anti-HCC immunity and extends the mouse survival rates. MR: Rates of liver cancer are on the rise in Western countries largely due to obesity and 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.	*None to date*
CA150590/P1/ P2/P3/P4 $1,323,046 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. As of year 1, transgenic pigs are generated and ready for characterization. Tumors have been developed and resected in multiple pigs; characterization and staging of tumors is ongoing. Tumors are also being monitored through imaging protocols. MR: HCC is exceedingly common in the U.S. Veteran population due to a high incidence of alcoholic cirrhosis and viral hepatitis.	*Presentations: 5* *Publication: 3* *Miscellaneous: 1* ***Start-up company based off of this technology was initiated*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
LIVER CANCER				
CA150850 $108,969 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.	*None to date*
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. MR: U.S. military personnel have unique exposure-related risks associated with the development of HCC. Agent Orange, pesticides, industrial solvents, and polychlorinated biphenyl (PCB) are all militarily relevant agents associated with increased risk of HCC.	*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				
CA160216/P1/P2 $905,558 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 that drive biliary tract cancers. The research team aims to identify how FGFR mutations alter signaling and how these cells respond to FGFR inhibition. Additionally, the team will identify genetic mechanisms that contribute to acquired resistance to FGFR inhibition and develop therapeutic strategies to prevent or overcome resistance. Currently, multiple cell lines with different FGFR mutations have been created, and they have identified additional cell lines that are resistant to FGFR inhibitors. 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.	*New research – no outcomes reported to date*
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. MR: Liver cancer (HCC) is recognized by the VA as a risk factor related to hepatitis C virus (HCV) infection or ionizing radiation exposure during military service.	*New research – no outcomes reported to date*
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. 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.	*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				
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 HCC therapies. Using cholangiocarcinoma and 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. MR: Cholangiocarcinoma (CAA) is the second most common primary liver cancer and it arises most frequently during the presence of chronic liver disease, affecting U.S. 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.	*New research – no outcomes reported to date*
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 gives 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. 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.	*New research – no outcomes reported to date*
CA170048 $563,949 Under Neg	Sarkar/ Virginia Commonwealth University	TAF2: A Potential Oncogene for Hepatocellular Carcinoma (HCC)	RP: To study the role of TAF2 as an oncogene in HCC and determine if it is a potential target for therapeutics. The investigators will do this by overexpressing and deleting TAF2 in cultured HCC cells and in mice. Then they will use patient-derived HCC tumor samples to establish HCC in mice and use siRNA to block TAF2 in vivo. MR: Incidence of HCC in the Veteran population has been increasing from 2001-2013 due to non-alcoholic fatty liver disease and alcoholic cirrhosis.	*Research not yet initiated*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
LIVER CANCER				
CA170103 $669,999 Open	Wajapeyee/ Yale University	A Druggable Epigenetic Vulnerability Pathway in p53-Deficient Hepatocellular Carcinoma	RP: Explore the therapeutic potential of DOT1L, an epigenetic regulator as a target for treating certain populations of HCC. The project will investigate the in vivo role of DOT1L in maintaining HCC tumor growth and metastasis and evaluate the utility of pharmacological targeting of DOT1L. MR: HCC is significantly higher in military personnel compared to the general population due to exposure to liver carcinogens while on duty locations.	*Research not yet initiated*
CA170172 $639,600 Under Neg	Nieto/ University of Illinois at Chicago	Role of Osteopontin in Hepatocellular Carcinoma	RP: A project to examine the biological contribution of osteopontin (OPN) to HCC. The PI will utilize well-established mouse models of HCC to investigate the impact of OPN in vivo. MR: HCC remains difficult to treat and the only approved oral treatment (Sorafenib) prolongs the median lifespan by about 2 months; this project could identify new potential targets for future treatment.	*Research not yet initiated*
CA170574 $533,188 Under Neg	Ploss/ Princeton University	Modeling Human Hepatocellular Carcinoma in Humanized Mice	RP: To understand the role that various mutations play in the formation and growth of HCC, with the hope of identifying targeted therapeutics for it. The investigator plans to engraft human liver cells in mice, then use CRISPR technology to disrupt genes commonly associated with the development of HCC to study the molecular processes involved in HCC development. MR: Incidence of liver cancer has been increasing from 2001-2013 in the Veteran population.	*Research not yet initiated*
CA170674 $1,114,344 Under Neg	Marks/ Naval Medical Center, San Diego Sirlin/ University of California, San Diego Loomba/ University of California, San Diego	Abbreviated Magnetic Resonance Imaging and Biomarker-Based Detection of Early Liver Cancer	RP: A prospective study to compare a newly developed scanning method for HCC detection. The team of researchers will compare diagnostic accuracy between conventional ultrasound screening and their new abbreviated MRI (AMRI) method for 200 patients, military and civilian, with chronic liver disease. MR: Growing evidence indicates that both HCC and its major risk factors, including alcoholism and hepatitis C and chronic hepatitis B infection, disproportionally affect the military population, beneficiaries, and U.S. Veterans.	*Research not yet initiated*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
LIVER CANCER				
CA170694 $558,000 Under Neg	Burgoyne/ University of California, San Diego	Development of a Cellular State Prediction Model of Sensitivity and Resistance to Dual PI3K/BET Inhibitors in Hepatocellular Carcinoma	RP: A project to refine a new classification system for HCC tumors for the purpose of predicting drug sensitivity. The PI will utilize drug responsive and resistant tumor cells from HCC patients to improve the accuracy of their predictive model and identify cellular targets that may be contributing to drug resistance. MR: The prevalence of HCV is at least twofold higher in the Veteran population in comparison to the general U.S. population, and two-thirds of Veterans with HCC are infected with HCV.	*Research not yet initiated*
CA171017 $572,400 Under Neg	Smoot/ Mayo Clinic and Foundation, Rochester	Mechanisms of Oncogenesis in the Primary Liver Cell Cancer Cholangiocarcinoma	RP: This study will identify whether members of the Src family of kinases are able to regulate signaling pathways, which are associated with cholangiocarcinoma, a specific type of liver cancer. MR: The U.S. Veteran population has a higher prevalence of hepatitis C infection than the general U.S. population. This infection doubles the risk of developing the liver cancer known as cholangiocarcinoma.	*Research not yet 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 exposure to cytotoxin and chemicals. DLBCL is one of the most aggressive and chemoresistant forms of NHL.	*New research - no outcomes reported to date*

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.	*New research - no outcomes reported to date*
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.	*New research - no outcomes reported to date*
CA170783 $692,000 Open	Kwak/ City of Hope Beckman Research Institute	Novel CAR-T Therapy Targeting BAFF-R Against B-Cell Lymphomas	RP: To develop a new CAR T cell therapy for patients with B-cell NHL. MR: Military personnel have greater risk of lymphoma due to deployment-related exposures. CAR T therapy has the potential to cure lymphomas.	*Research not yet initiated*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
LYMPHOMA				
CA170924/P1/P3 $1,159,665 Under Neg	Ansell/ Mayo Clinic and Foundation, Rochester Lazaryan/ University of Minnesota Twin Cities Villasboas Bisneto/Mayo Clinic and Foundation, Rochester	Promoting an Effective Antitumor Immune Response in Lymphoma	RP: To use the activation of suppressed effector cells and immune exhausted T-cells to induce an effective antitumor response in B-cell NHL. MR: Military personnel are at greater risk for developing NHL due to exposure to cytotoxins and chemicals during deployment. This study will enhance the intrinsic immune function to mount an effective antitumor immune response.	*Research not yet initiated*
CA171169 $575,997 Under Neg	Leeman-Neill/ Columbia University Medical Center	The Role of Activation-Induced Cytidine Deaminase in Pesticide-Related Lymphomagenesis	RP: To evaluate the effects of pesticides on AID-mediated mutagenesis and lymphomagenesis and to elucidate the mechanism linking pesticide exposure to increased AID expression and aberrant somatic hypermutation. MR: Military personnel experience a significant degree of pesticide exposure and have been found to experience adverse health effects due to pesticide exposures.	*Research not yet initiated*
MELANOMA/SKIN CANCER				
CA130316 $446,860 POP EXP	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. Identified miRNAs that are expressed in melanocytes, but not skin keratinocytes or fibroblasts, and identified a miRNA network that regulates melanoma tumor progression that may be used as a prognostic marker. In melanocytes that express the oncogenic BRAF V600E mutation, loss of miR-211 stimulates growth of melanocytes while overexpression of Let-7i inhibits melanoma growth. PI has identified a UV-regulated miRNAs that could potentially be used as biomarkers in predicting prognostic outcome in melanoma patients. 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.	*Presentations: 3* *Degrees Obtained: 1* *Publications: 3*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
MELANOMA/SKIN CANCER				
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 melanomagenesis 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 seems to be due to the loss of Dot1L participation in DNA damage repair. MR: Individuals serving in tropical areas that receive heavy sun exposure during their early adulthood may be at higher risk of developing melanoma later in life.	*Publication: 1*
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 from this study suggest that TIGIT is overexpressed in T regulatory cells (Tregs) located in close proximity to the tumor site. Tregs expressing TIGIT are more immunosuppressive than those lacking TIGIT expression. There is also an inverse correlation between more immunosuppressive Tregs and expression of CD226, an immune-stimulatory protein competing for the same ligand as TIGIT. The knowledge of this expression pattern could lead to potential new therapies that target these proteins to alleviate 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: 4*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
MELANOMA/SKIN CANCER				
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 2 years of the award, the PI has shown that PD-L1, one of the top targets for new antitumor immunotherapies, is highly expressed within tumor-associated lymphatic vessels. 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 and treatment response 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: 3* *Presentations: 9* *Funding Applied for: 1*
CA140216 $460,477 Open	Harbour/ University of Miami Coral Gables	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 resulting 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.	*Presentation: 1*
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 to 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: 2* *Presentations: 5* *Miscellaneous: 2*
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 U.S. military receive high exposure to solar UV radiation due to their training and deployment in sunny environments, increasing their risk of melanoma.	*Presentation: 1*
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 shows that FUS can increase immune response in tumor-bearing mice. Optimizing tumor clearance and survival upon FUS stimulation with or without combinatorial therapy will be the focus of the next year of funding. MR: The incidence of melanoma is higher in the U.S. military population than in the U.S. population as a whole. Improvement to the current standard of care would therefore affect military families preferentially.	*Presentations: 5* *Funding Obtained: 1* *Funding Applied for: 1*

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 targeted 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 melanoma lung metastasis. The PI has shown that his particles have cyctotoxic activity only upon exposure to X-rays. The PI is currently optimizing his particles to enhance tumor targeting. 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: 10* *Presentations: 4*
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 (PHF), a promising new compound for UV-induced cancer prevention. Preliminary experiments demonstrate a protective effect against UV-induced damage in the presence of PHF formulations. Sustained-release particles 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* *Miscellaneous: 1* *Funding Applied for: 1*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
MELANOMA/SKIN CANCER				
CA150055 $631,883 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. The PI is currently investigating a newly developed class of antioxidants for their ability to prevent UV-induced DNA damage. Initial studies support the hypothesis that these compounds can protect against UVB induced cytotoxicity. 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.	*Publication: 1*
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. In vivo testing of nanoparticle vaccines shows that they are able to promote T-cell activation to melanoma-specific antigens. Year 2 of the project will test the therapeutic efficacy of nanoparticle vaccines compared to immune checkpoint inhibitor therapy. MR: Melanoma is of particular interest to the U.S. 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.	*Presentations: 5* *Publication: 3*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
MELANOMA/SKIN CANCER				
CA150197 $657,255 Open	Zheng/ Massachusetts General Hospital	Role of the Lipid Phosphatase INPP48 in the Development of Resistance to BRAF Pathway Inhibition	RP: This project will 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. Within the first year of the award, the PI has confirmed that reduced INPP4B expression significantly decreased the sensitivities of melanoma cells (A375, SKMEL28, Colo829) to the treatment of BRAF inhibitors in cell viabilities assays. 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 U.S. population.	*None to date*
CA150256 $617,020 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.	*Publication: 1*
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. From initial data, ARID2 looks to act as a robust transcriptional repressor, which may account for its potential tumor suppressor activities. 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.	*Presentation: 1*

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. In the first year of the award, the PI has confirmed that cell lines with induced BRAF inhibitor resistance have higher polyamine transport activity. A novel drug developed by the research team that targets the polyamine transport system inhibits the growth of melanoma cells in vivo and may slow the occurrence of BRAF inhibitor resistance. 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.	*Presentation: 1* *Publication: 1* *Patent: 1*
CA150391 $605,018 Open	Wang/ University of North Carolina at Chapel Hill	Tissue-Engineered Cancer Metastasis to Improve the Abscopal Effect and Cancer Immunotherapy in Melanoma	RP: This project will investigate the utility of using irradiated melanoma lung metastasis (mets) as an immunizing agent to stimulate an anti-cancer response in tumor-bearing mice. In the first year of the award, the PI has established procedures for testing his vaccine in mice. The second year of the award will focus on optimizing the response to irradiated lung mets. 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 Forces.	*None to date*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
MELANOMA/SKIN CANCER				
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 to date*
CA150492 $632,000 POP EXP	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 for the general public.	*Presentations: 2*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
MELANOMA/SKIN CANCER				
CA150523 $528,801 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. The PI has initiated this work and successfully developed her drug-conjugated nanoparticles. In the coming years, she will be testing their *in vivo* activity. MR: Melanoma disproportionately affects U.S. military personnel, suggesting a role for military Service-related exposure to carcinogens.	*Publications: 2*
CA150619/P1/P2 $720,000 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. Mouse models have been created to study the immune response to human melanoma and how immunotherapies affect immune cell infiltration into the tumors. MR: Eighty-five percent of all melanomas are induced by excessive sun exposure, an environmental hazard many members of the military have had to confront for the last 15 years. Starting in the near future, the incidence of melanoma (and other skin cancers) is expected to drastically increase in active duty members and Veterans.	*None to date*
CA150630/P1/P2 $1,520,000 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). The dose escalation trial is expected to complete in year 2, after which time analysis on antibody effect will begin. MR: Active duty 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 U.S. military is currently engaged.	*None to date*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
MELANOMA/SKIN CANCER				
CA150804 $127,125 Open	Ribeiro Muniz/ Icahn School of Medicine at Mount Sinai	Endogenous Alarmins in the Progression of Melanoma	RP: The project will identify the receptors involved in metalloproteinase 2 (MMP-2) signaling and investigate the mechanisms by which MMP-2 promotes melanoma progression. In the first year of the award, the PI has determined that MMP-2 directly interacts with TLR2 and TLR4, both of which are required for MMP-2 induced signaling. Both tumor incidence and tumor growth were reduced in mice that received bone marrow cells lacking TLR2 and TLR4 when compared with WT recipients suggesting that loss or inhibition of these receptors could be protective against melanoma development. 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.	*Presentations: 2*
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.	*New research – no outcomes reported to date*
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.	*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				
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.	*New research – no outcomes reported to date*
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.	*New research – no outcomes reported to date*
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.	*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				
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.	*New research – no outcomes reported to date*
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.	*New research – no outcomes reported to date*
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.	*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				
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.	*New research – no outcomes reported to date*
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.	*New research – no outcomes reported to date*
CA170340 $644,000 Under Neg	Xu/ University of Pennsylvania	Exosomal PD-L1 Mediates Tumor Immunosuppression	RP: Melanoma cells secrete vesicles called exosomes that express the inhibitory protein PD-L1. The investigators plan to determine the role of exosomal PD-L1 in inhibiting antitumor T cell function in melanoma, and whether the presence of the exosomes are a biomarker that predicts tumor burden and immune response in melanoma patients. MR: This study concerns a type of cancer that is related to the environmental carcinogen ultraviolet light. 85% of all melanomas are induced by excessive sun exposure, which many members of the military have had to endure over the last 15 years. Starting in the near future, we expect that the incidence of melanoma (and other skin cancers) will drastically increase in active duty members and Veterans.	*Research not yet initiated*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
MELANOMA/SKIN CANCER				
CA170374/P1/P2 $1,249,214 Under Neg	Gershenwald/ Davies/ Tetzlaff/ The University of Texas MD Anderson Cancer Center	Integration of Clinical, Molecular, and Immune Features to Improve Risk Stratification and Outcomes in Melanoma Patients with Sentinel Lymph Node Metastasis	RP: A project to optimize and validate predictive clinical outcome models for stage III melanoma patients to improve patient management strategies. MR: Melanoma is the second most commonly diagnosed cancer among active men and women in the U.S. military.	*Research not yet initiated*
CA170483/P1 $878,656 Open	Najjar/ Delgoffe/ University of Pittsburgh	Metabolic Remodeling of the Tumor Microenvironment to Improve the Efficacy of Immunotherapy	RP: A study to describe the effect of a novel combination therapy on immune cell function. The PI will obtain samples from a clinical trial enrolling melanoma patients, examine the effect of anti-PD1 therapy in combination with the type-2 diabetes drug metformin, and compare the immune cell characteristics in patients given the combination or monotherapy. MR: Melanoma is the most commonly diagnosed cancer in the VA population.	*Research not yet initiated*
CA170628 $624,000 Under Neg	Lombard/ University of Michigan, Ann Arbor	Targeting the Menin-MLL1 Interaction in Melanoma	RP: A project to investigate whether inhibitors to the scaffold protein Menin may prove efficacious as novel treatments for melanoma. The PI will examine the anti-cancer effect of the drugs on cell lines as well as in mouse models of melanoma. MR: Active duty military personnel suffer up to a 62% increased incidence of melanoma relative to the general population.	*Research not yet initiated*
CA170653 $688,000 Open	Smalley/ H. Lee Moffitt Cancer Center & Research Institute	Improving Therapy for Melanoma Brain Metastases	RP: A project to determine how the cross-talk between melanoma cells and the brain leads to changes at the molecular level that facilitate acquired resistance to therapy. The PI will use both mouse models of melanoma brain metastasis and patient samples to help describe these adaptive changes. MR: U.S. military personnel often operate under conditions of high ultraviolet (UV) exposure, one of the major environmental risk factors for melanoma development.	*Research not yet initiated*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
MELANOMA/SKIN CANCER				
CA171012 $540,343 Under Neg	Fallahi-Sichani/ University of Michigan, Ann Arbor	Defining and Targeting Novel Epigenetic Vulnerabilities in Heterogeneous Drug-Resistant Melanomas	RP: To define the epigenetic states that contribute to kinase inhibitor resistance in melanoma. The PI aims to identify the key epigenetic regulators in vitro and validate their role in drug resistance in vivo. MR: Melanoma is the deadliest form of skin cancer, which shows a higher incidence rate in active duty military personnel as compared with the general population, most likely due to their longer exposure to UV ionizing radiation.	*Research not yet initiated*
CA171013 $476,000 Under Neg	Ronai/ Technion Research and Development Foundation Ltd.	Siah2 Ubiquitin Ligase in Immune Checkpoint and Melanomagenesis	RP: This project aims to characterize the role of Siah2, a ubiquitin ligase, in regulating the immune response to melanoma. Results from this project will identify (1) which immune cells are most affected by Siah2 loss and (2) Siah2-dependent pathways critical for regulating immune cell function in vitro and in vivo. MR: There is an urgent need for effective melanoma treatments. This disease is highly relevant to military personnel given the key role of sunlight in the etiology of melanoma.	*Research not yet initiated*
CA171014 $594,000 Under Neg	Yusuf/ University of Alabama at Birmingham	Pharmacological Management of Ultraviolet Radiation-Induced Skin Cancer	RP: A project to investigate the mechanism by which the Toll-like receptor-4 antagonist TAK-242 regulates inflammation and prevents UV-induced oncogenesis. MR: Exposure to solar radiation and extremes of temperature and humidity all contribute to the high prevalence of cutaneous disease in military personnel	*Research not yet initiated*
CA171043 $648,923 Under Neg	Hernando-Monge/ New York University School of Medicine	Identification of Glycomic Alterations During Melanoma Metastasis	RP: This project aims to identify glycosylation signatures that (1) promote melanoma brain metastasis and (2) can be used as prognostic indicators of patient outcomes. MR: Melanoma incidence is increasing within military workforces deployed in regions of elevated sun exposure, and, in about 30% of patients, cutaneous tumors spread through other organs.	*Research not yet initiated*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
MELANOMA/SKIN CANCER				
CA171056 $624,000 Under Neg	Aplin/ Thomas Jefferson University	Optimizing Targeted Therapies for Wild-Type BRAF, Wild-Type NRAS (WT/WT) Melanoma	RP: A project to identify the mechanisms of adaptive resistance to kinase inhibitor therapy in melanomas. Using both in vitro single-cell approaches as well as employing patient-derived cell organoids and xenograft models, the PI will investigate whether co-targeting multiple protein kinases could be a more effective therapeutic strategy. MR: As stated in the Medical Surveillance Monthly report for February 2017, during the last 15 years of study (1 January 2001 through 31 December 2015), the incidence of malignant melanoma in U.S. military personnel increases in an exponential manner through years of service.	*Research not yet initiated*
CA171106 $550,980 Open	Bardhan/ Vanderbilt University	Multiplexed Immunomarker Screening to Enable Patient-Tailored Immunotherapies	RP: A study to develop imaging tools to measure PD-L1 and other biomarker expression within melanoma tumors. The PI will then examine if these imaging tools are able to predict immunotherapy sensitivity in mice based upon their biomarker status. MR: Accurate predictive tools to ensure that the right patient receives the right therapy is a significant unmet clinical need.	*Research not yet initiated*
CA171123 $550,800 Under Neg	Gaddameedhi/ Washington State University, Pullman	Harnessing the Circadian Clock to Alleviate Ionizing Radiation-Induced Toxicity During Melanoma Therapy	RP: A project to investigate whether there is a connection between circadian clock function and the effectiveness of radiation therapy. In vitro and in vivo models will be utilized to determine whether active circadian rhythm has a protective role against the adverse effects of radiation treatment alone or in combination with immunotherapy. MR: The incidence of melanoma in active duty military personnel has been increasing and now exceeds that of the general population.	*Research not yet initiated*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
MELANOMA/SKIN CANCER				
CA171179 $622,002 Under Neg	Jimeno/ University of Colorado at Denver	Modeling Neoantigen and TCR Dynamics in Melanoma and Its Role in Acquired Resistance to Immunotherapy Using Autologous Thymus-Bearing Humanized Mice	RP: This project aims to establish a benchmark for neoantigen content in melanoma tumors and to define patterns associated with innate and acquired resistance during the course of immune-directed therapy. MR: This study addresses both the focus area of military-relevant etiologic factors, as well as unmet gaps in the treatment of conditions, especially given that melanoma prevalence in military populations exceeds that of civilian populations.	*Research not yet initiated*
CA171198 $702,000 Under Neg	Tinoco/ Sanford-Burnham Medical Research Institute, La Jolla	Targeting the PSGL-1 Immune Checkpoint to Promote Melanoma Tumor Control	RP: To investigate the role of P-selectin glycoprotein 1 (PSGL-1) signaling in antitumor T cell inhibition. Goal is to develop an immunotherapy to block PSGL-1, which will activate immune cells to target the tumor. First, they plan to delete PSGL-1 in mice and investigate how this receptor affects immune cell development and function. Second, they will block PSGL-1 in mice to determine if the T cells will control the tumor. MR: Rates of melanoma are higher for military members compared to the general population, with the rate increasing among younger men in the military, particularly the Air Force.	*Research not yet initiated*
MESOTHELIOMA				
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 shows a significant reduction in tumor growth in co-culture systems. When transferred to malignant mesothelioma bearing mice, the anti-tumor effect of the NK cells lacking EphA2 was significantly greater than wild type NK cells. Furthermore, this therapy not only slowed tumor growth but also induced apoptotic clearance of the tumors. 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: 2*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
MESOTHELIOMA				
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.	*Presentation - 1*
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. Gene variants will be identified in year 1 of this award, and the PI will follow-up in year 2 with in vivo testing to determine the effect of these variants on asbestos carcinogenesis. MR: The majority of U.S. Veterans were exposed to asbestos at some point during their military service in shipyards, aircraft, etc. Indeed, malignant mesothelioma is disproportionally overrepresented in the military as Veterans account for nearly one-third of all malignant mesothelioma diagnoses.	*None to date*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
MESOTHELIOMA				
CA150300 $552,343 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. Two versions of the mouse-specific vaccine were generated and tested in year 1 showing a promising effect on tumor growth and mouse survival. A third iteration will be developed and tested in year 2 and the most effective vaccine will be used for characterization. Development and evaluation of a human specific Tvax is also proposed for year 3. MR: More than 300 products, e.g., valves, brakes, gaskets, cements, adhesives, and pipe coverings, containing asbestos, were used by the military, primarily 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.	*Presentation: 1*

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MESOTHELIOMA				
CA150671/P1/ P2/P3/P4 $1,249,214 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. The investigators have developed HMGB1 knockout mouse models and are currently performing long-term studies to assess whether HMGB1 expression is critical for MM following asbestos exposure and whether disruption of HMGB1 signaling is a viable intervention target. The project is also developing protocols to 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 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.	*None to date*
CA150787 $73,435 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 MM as targets for cancer immunotherapies. The work in the first year of the award supports the hypothesis that tumor-specific antigens can be used as prophylactic cancer vaccines. The following year will determine whether vaccination against these antigens can sensitize MM mice to other therapies. 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 U.S., Veterans of the military account for nearly one-third of all MM diagnoses.	*Presentation: 1* *Publication: 1*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
MESOTHELIOMA				
CA160250 $622,000 Open	Heasley/ University of Colorado at 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 U.S. 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.	*New research – no outcomes reported to date*
CA160891/P1 $1,491,517 779,375 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.	*New research – no outcomes reported to date*
CA170299 $394,281 Under Neg	Lake/ University of Western Australia	The MexTAg Collaborative Cross: Understanding Genetic Modifiers in Mesothelioma	RP: This study aims to identify genes that promote or protect against mesothelioma. The investigators will use a new mouse model that develops mesothelioma after exposure to asbestos. They will study the progression of mesothelioma in these mice, as well as which genes are involved, and then use mesothelioma datasets to determine the human genetic equivalents. MR: U.S. Veterans, who make up 30% of mesothelioma deaths in the U.S., are exposed to asbestos while deployed in the Middle East.	*Research not yet initiated*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
MESOTHELIOMA				
CA170319 $539,500 Open	Viapiano/ State University of New York Upstate Medical University	A Theranostic Antibody-Cytokine Reagent for Diagnosis and Multipronged Therapy of Malignant Mesothelioma	RP: A project to develop a dual diagnostic and targeted therapeutic for MM. The PI will engineer and characterize an IL2-conjugated anti-fibulin3 antibody for ability to treat MM in vivo. A gadolinium-labeled version will also be generated for detection of tumor burden by MRI. MR: Historical exposure to asbestos in U.S. military installations and vehicles, or combat zones in the 1960s-1990s, has resulted in a much higher incidence of MM in military Veterans compared to the general population.	*Research not yet initiated*
CA170630 $638,739 Open	Adusumilli/ Memorial Sloan Kettering Cancer Center	Cell-Selective, Repetitive, Irreversible Electroporation to Augment Mesothelioma CAR T-Cell Therapy	RP: PI has previously developed CAR-T cells that target mesothelin, a protein that is overexpressed on mesothelioma cells. In this study, they will determine if a technique called irreversible electroporation can help the antitumor T cells localize to the tumor site more efficiently. MR: U.S. Veterans, who make up 30% of mesothelioma deaths in the U.S., are exposed to asbestos while deployed in the Middle East.	*Research not yet initiated*
MYELOPROLIFERATIVE DISORDERS				
CA150085 $551,362 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 Warfighters combat these diseases.	*None to date*
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.	*None to date*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
MYELOPROLIFERATIVE DISORDERS				
CA150529 $691,744 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 damage to the bone marrow. This study will lead to new drug targets to radiation-induced MPNs.	*None to date*
NEUROBLASTOMA (NB)				
CA140035 $570,601 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 NB. Novel therapeutics targeting these molecules will benefit children of military families and active Service members/Veterans.	*None to date*
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-β 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 NB.	*Publications: 2*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
NEUROBLASTOMA (NB)				
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 NB. 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 NB would undoubtedly benefit the most from the potential treatment options that arise from this proposal.	*None to date*
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 NB, 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 NB 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.	*None to date*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
NEUROBLASTOMA (NB)				
CA150773 $122,979 POP EXP	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 NB by (1) mapping ATRX binding sites in wild-type NB and comparing 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. Through interrogation of the unexplored epigenetic mechanisms that contribute to aggressive NB, the PI aims to develop rational therapies to better manage the burden of disease.	*Presentation: 1* *Publication: 1*
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 NB 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 NB 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 NB 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.	*New research - no outcomes reported to date*
CA170257/P1 $1,702,500 Under Neg	Hogarty/ Asgharzadeh Children's Hospital, Philadelphia	Altering the Tumor Microenvironment to Augment Neuroblastoma Immunotherapy	RP: The goal of this TTSA is to test the hypothesis that the solid tumor microenvironment (TME) is a byproduct of the specific oncogenes driving the cancer, and that NBs with different driver mutations will have distinct immunosuppressive TMEs. MR: Children of military personnel are often affected as NB is the most common childhood solid tumor, and the stress of having a critically ill child negatively impacts the military readiness of Armed Forces.	*Research not yet initiated*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
NEUROBLASTOMA (NB)				
CA171026 $717,986 Under Neg	Freeman/ St. Jude Children's Research Hospital	Investigating the Downstream Oncogenic Consequences and Therapeutic Susceptibilities Caused by Loss of ARID1A in Neuroblastoma	RP: PI will test the hypothesis that ARID1A is a predominant 1p36 tumor suppressor whose loss relieves N-Myc-induced replication stress in NB, and that loss of ARID1A via 1p36 deletion in a model of NB will recapitulate the drug sensitivities of ARID1A-mutated cancers. MR: The military relevance focus of this proposal is to advance better treatment for NB patients that are dependents of military personnel and Veterans.	*Research not yet initiated*
PANCREATIC CANCER				
CA130288 $415,200 POP EXP	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 to be 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: 5* *Presentations: 27*
CA140731 $403,459 Open	Der/ University of North Carolina at Chapel Hill	Targeting KRAS for Pancreatic Cancer Treatment	RP: To fully define K-RAS 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 the most frequently 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 U.S. active Service members and their families, with only a 6% 5-year survival rate.	*Presentations: 4* *Publications: 4* *Miscellaneous: 2* *Funding Obtained: 2*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
PANCREATIC CANCER				
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 (aCTLA-4, aPD-1, and a4-1BB) can successfully activate an immune response against pancreatic cancer. The PI found that, in a mouse model of pancreatic cancer, a4-1BB alone results in liver toxicity. However, therapy combining anti-CTLA-4 and 4-1BB antibodies with an immune stimulatory molecule (a STING agonist) extended mouse survival and reduced toxicity. This effect appears to be due to aCTLA-4 indirectly enhancing the role of regulatory T cells in the liver. MR: Pancreatic cancer is one of the most lethal forms of cancer affecting Service members, Veterans, and military beneficiaries and their families.	*Presentations: 4* *Publication: 1*
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 activate CD4 T cells outside of the pancreas, in the lymph nodes and spleen, and then have those T cells infiltrate the pancreatic tumor and trigger 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.	*None to date*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
PANCREATIC CANCER				
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 who are currently serving or who may have served in the military as opposed to a presumed link to a military occupational exposure.	*None to date*
CA150626/P1/ P2/P3/P4 $1,567,577 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.	*None 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.	*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				
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 U.S. 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.	*New research – no outcomes reported to date*
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 U.S. Veteran population, by virtue of its increased excessive use of tobacco and alcohol, is more prone to pancreatic cancer.	*New research – no outcomes reported to date*
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).	*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				
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 disproportionately represented in the military.	*New research – no outcomes reported to date*
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.	*New research – no outcomes reported to date*
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.	*New research – no outcomes reported to date*
CA170314 $620,000 Under Neg	Mo/ University of Mississippi Medical Center	Identification of lncRNAs Required for Synthetic Lethal Interactions with Mutant KRAS in Pancreatic Cancer	RP: The PI hypothesizes that long non-coding RNAs (lncRNAs) play an important role in regulating the RAS pathway. The goal of this project is to identify these regulatory lncRNAs and determine their role in pancreatic cancer pathogenesis. MR: The success of this study will have a great impact on pancreatic cancer diagnosis and therapy and will thus benefit those, especially military personnel, who suffer from this devastating disease.	*Research not yet initiated*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
PANCREATIC CANCER				
CA170450 $678,000 Under Neg	Miller/ New York University School of Medicine	Investigating the Role of Piezo1 in Pancreatic Cancer-Related Immune Suppression and Disease Progression	RP: The PI will study the role of a mechano-sensitive ion channel (Piezo1) in promoting immune tolerance, and thus tumor growth, in pancreatic adenocarcinoma (PDAC). He will also test whether inhibiting Piezo1 enables efficacy of checkpoint-based immunotherapy in PDAC. MR: PDAC is the third leading cause of cancer-related death in the U.S.; there are few long-term survivors. Several studies have found an increased risk of pancreatic cancer in Veterans who were deployed overseas during the Vietnam War, and Veterans with diabetes have particularly increased risks of developing pancreatic cancer.	*Research not yet initiated*
CA170568 $490,258 Under Neg	Fridman/ Wayne State University	Disrupting Collagen-Mediated Prosurvival Pathways in Pancreatic Cancer	RP: PI will assess the role of Discoidin Domain Receptor (DDR) kinases, major family of collagen receptors, in mediating resistance of pancreatic tumors to MEK inhibition. He will test the hypothesis that disrupting DDR function by pharmacological or genetic means may attenuate PDAC pro-survival/fibrotic pathways and enhance therapeutic efficacy drugs targeting Kras-driven (MEK) signaling networks. MR: Two of the major risk behaviors associated with developing pancreatic cancer (smoking and alcohol abuse) are observed more often in military members who have experienced combat as compared to the general public.	*Research not yet initiated*
CA170974/P1/P2 $1,721,374 Under Neg	Chung; Pandol/ Cedars-Sinai Medical Center Tomlinson/ University of California, Los Angeles	Sensitization of Therapeutic-Resistant Pancreatic Cancer by Cancer Cell-Specific Drug Delivery	RP: The PI's team will (1) assess whether a pancreatic tumor-specific drug, heptamethine carbocyanine, and simvastatin (HMCD-SIM), can resensitize pancreatic ductal adenocarcinoma (PDAC) tumors to chemotherapy, and (2) determine the mechanisms of action for HMCD-SIM. Additonally, the team will assess the use of G protein coupled receptor-associated sorting protein 1 (GASP-1) as a biomarker for early detection of PDAC. MR: The combination of the poor prognosis of pancreatic cancer (only a 7% 5-year survival rate) and increasing evidence that military service increases a person's risk for developing pancreatic cancer results in an increased burden to the Military Health System.	*Research not yet initiated*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
PANCREATIC CANCER				
CA171001 $554,400 Under Neg	Sherman/ Oregon Health & Science University	Understanding Stromal Fibroblast Heterogeneity in the Pancreatic Tumor Microenvironment	RP: The PI will assess the contribution of pancreatic stellate cells (PSCs) to the pancreatic ductal adenocarcinoma (PDAC) microenvironment, analyze the interactions between PSC-derived cancer-associated fibroblasts (CAFs) and PDAC cells, and understand the significance of PSC homeostasis during PDAC progression. MR: Veterans have an increased risk of developing pancreatic cancer due, in part, to the associations between alcohol use and pancreatic cancer risk, and between diabetes and pancreatic cancer risk.	*Research not yet initiated*
PEDIATRIC BRAIN TUMOR				
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 ionizing radiation 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: 2* *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 the 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.	*Publications: 4* *Presentation: 1*

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.	*New research – no outcomes reported to date*
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.	*New research – no outcomes reported to date*
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.	*New research – no outcomes reported to date*

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 of improving immune cell response in DIPG. MR: To date DIPG is an incurable disease that adversely affects the preparedness of our military.	*New research – no outcomes reported to date*
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.	*New research – no outcomes reported to date*
CA170414 $536,431 Under Neg	Mulcahy Levy/ University of Colorado at Denver	Optimization of Autophagy Inhibition as a Clinical Target for Brain Tumors	RP: The PI will define how and why autophagy inhibition is effective in RAF pathway-driven central nervous system (CNS) tumors, how best to inhibit the pathway, and what additional biomarkers might be available for autophagy dependence to plan effective future autophagy inhibition trials and improve the survival of CNS tumor patients. MR: RAF pathway-driven CNS tumors affect children, adolescents, and adults. Improving the care of these patients will enable Service members to more rapidly return to service as the time needed for intensive care of themselves or their dependents will be lowered, enabling them to balance the needs of their families with the needs of their service position.	*Research not yet initiated.*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
PEDIATRIC BRAIN TUMOR				
CA170677 $622,000 Under Neg	Vibhakar/ University of Colorado at Denver	SIRT2 as an Epigenetic Vulnerability in Atypical Teratoid Rhabdoid Tumors	RP: The goal of this project is to determine the molecular mechanisms by which the deacetylase SIRT2 drives atypical teratoid rhabdoid tumor (ATRT) formation and to provide preclinical validation of SIRT2 inhibition as a therapeutic approach in treating ATRT. MR: ATRT is an aggressive and malignant pediatric brain tumor. Current therapies are not optimal and leave children with many long-term side effects. These issues require significant resources and family time. 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.	*Research not yet initiated.*
CA170822 $655,000 Under Neg	Raabe/ Johns Hopkins University	Targeting Abnormal Epigenetics in Diffuse Intrinsic Pontine Glioma by Inhibiting TET Enzymes	RP: The PI will test the hypothesis that inhibition of TET enzymes will lead to reduced levels of the epigenetic modification 5hmC, restored epigenetic balance, decreased tumorigenicity, and increased sensitivity to radiation and chemotherapy. MR: The preponderance of young people and parents in active duty military means that pediatric and young adult brain tumors have a disproportionate impact on the health and well-being of military Service members and their dependents. Diffuse midline gliomas including diffuse intrinsic pontine glioma (DIPG) largely affect children and young adults and have a 100% mortality rate.	*Research not yet initiated.*
CA171021 $589,500 Under Neg	Rubens/ Johns Hopkins University	Targeting Oncoprotein-Adapted Amino Acid Metabolism in Atypical Teratoid Rhabdoid Tumors	RP: The PI will test the hypothesis that the transcriptional regulator MYC drives adaptations in amino acid metabolism that can be pharmacologically targeted to improve survival in atypical teratoid rhabdoid tumors (AT/RT), a form of malignant brain tumors diagnosed in infancy. MR: Childhood cancer disproportionately affects military personnel and their families but is grossly underrepresented in government-supported research. A Service member coping with a child being treated for AT/RT, which only has a median survival of 6-11 months, negatively impacts mission readiness.	*Research not yet initiated.*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
PEDIATRIC BRAIN TUMOR				
CA171067 $577,611 Under Neg	Thompson/ Duke University	The Role of CD155 in Leptomeningeal Dissemination and Oncolytic Virus Susceptibility in the Medulloblastoma Microenvironment	RP: The PI will test the hypothesis that the oncolytic polio viral immunotherapy (PVSRIPO) will infect both solid tumor and metastatic leptomeningeal medulloblastoma cells in vivo, resulting in tumor cell killing and an ensuing innate and durable adaptive immune response. MR: Children of fathers who served in the Air Force are at increased brain tumor risk. Brain cancer, such as medulloblastoma, in a Warfighter or in a Warfighter's child can interfere with mission readiness.	*Research not yet initiated.*
CA171070 $620,000 Under Neg	Hinchcliffe/ University of Minnesota Twin Cities	Cellular Mechanisms Underlying Pediatric Glioblastoma: Heterozygous Mutations in Histone H3.3 Induce Chromosome Instability by Abolishing Ser31 Phosphorylation	RP: The PI will test the hypothesis that mutations in the N-terminal tail of histone H3 variant H3.3 deplete H3.3 phosphorylation on the amino acid Ser31, thereby inducing chromosome instability during cellular division. The resulting daughter cells are then susceptible to increasing rates of mutation because of their unbalanced genomes. MR: Pediatric brain cancer has a higher incidence in the military population, and the high-grade gliomas associated with our research are caused by somatic mutation – often caused by exposure to environmental toxins – themselves risk factors that are associated with military service.	*Research not yet initiated.*
CA171185 $577,200 Under Neg	Phoenix/ University of Cincinnati	Defining and Targeting the Blood-Brain Barrier in Pediatric Glioma Subgroups	RP: The objective of this proposal is to take an unbiased approach to define BBB function across pediatric glioma subgroups, and to determine if suppression of DIPG Wnt signaling will alter BBB function and improve drug efficacy. MR: Alterations in brain vasculature play an important role in neurological diseases, including brain tumors, stroke, head trauma, and neurodegenerative disorders. This research will advance our understanding of brain blood vessel properties and their dysfunction during disease, directly impacting Service members and their families.	*Research not yet initiated.*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
STOMACH CANCER				
CA150079 $586,758 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.	*Funding Obtained: 9*
CA150132 $396,000 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.	*None to date*
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.	*Publication: 1* *Presentation: 1*
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 *H. pylori* infection. This study could lead to new treatment options for stomach cancer.	*None to date*
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 *H. 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, one of the top cancers treated in the VA system.	*None to date*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
STOMACH CANCER				
CA150646/P1/P2 $1,322,311 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.	*None to date*
CA150647/P1/ P2/P3/P4 $1,535,985 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 *H. pylori* infection and radiation exposure resulting in increased risk of gastric cancer.	*None to date*
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.	*None to date*
CA150895 $131,250 POP EXP	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 *H. pylori* infection and radiation exposure, resulting in increased risk of gastric cancer.	*None to date*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
STOMACH CANCER				
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 *H. pylori.* This study may lead to the development of new therapeutics to stomach cancer.	*New research – no outcomes reported to date*
CA160431 $558,001 Open	El Zaatari/ University of Michigan, Ann Arbor	Targeting B Cell-Mediated Type II Autoimmunity in Gastric Carcinogenesis	RP: *H. 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.	*New research – no outcomes reported to date*
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 (1) immune suppression by upregulating immune checkpoint protein PDL1 and CD47 in tumor cells and (2) 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 *H. 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.	*New research – no outcomes reported to date*
CA160445/P1/P2 $1,598,400 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.	*New research – no outcomes reported to date*

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.	*New research – no outcomes reported to date*
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 ionizing radiation and to *H. pylori*. This study hopes to develop a biomarker-based treatment strategy for GC patients.	*New research – no outcomes reported to date*
CA160688 $518,400 Open	Wang/ University of California at 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 ionizing radiation and to *H. pylori*. This study hopes to develop a new biomarker and treatment strategy.	*New research – no outcomes reported to date*
CA160801 $619,375 Open	Korn/ University of California at 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 *H. pylori* infection and radiation exposure. This study will help to develop more efficacious treatments for this disease.	*New research – no outcomes reported to date*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
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.	*New research – no outcomes reported to date*
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 *H. pylori* infection and radiation exposure. This study will help to develop new inhibitors of CDK9 to treat GAC.	*New research – no outcomes reported to date*
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 GC. This study will provide a better understanding of the pathogenesis of GC by developing mouse models of this disease.	*New research – no outcomes reported to date*
CA170308 $620,041 Under Neg	Wilson/ Vanderbilt University Medical Center	Novel Intervention for Helicobacter pylori-Induced Stomach Cancer: Chemoprevention by Scavengers of Electrophiles	RP: To test the idea that electrophiles derived from *H. pylori*-induced gastric inflammation causes histone and DNA modification, thus causing genomic instability. MR: Military personnel are at higher risk for gastric cancer. This study is expected to lead to improved care for patients with *H. pylori* infection by reducing the development of gastric cancer and the associated socio-economic parameters in military and Veteran populations.	*Research not yet initiated*
CA170399 $616,018 Under Neg	Merrell/ Uniformed Services University of the Health Sciences	Helicobacter pylori-Induced DNA Double-Strand Breaks and Gastric Cancer	RP: To determine if R-loops are induced by *H. pylori* infection, and to determine whether blocking R-loop formation will decrease DNA damage. MR: Military Service members and Veterans have higher exposure to *H. Pylori* and are at increased risk of developing stomach cancer.	*Research not yet initiated*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
STOMACH CANCER				
CA170906 $640,000 Under Neg	Song/ The University of Texas MD Anderson Cancer Center	Discover Novel Biomarkers/Targets for Advanced Gastric Adenocarcinoma Patients by Exploring Tumor-Associated Exosomes from Malignant Ascites	RP: To characterize tumor-associated exosomes from PC supernatant by proteomic profiling to identify new biomarkers and to establish new therapeutic targets for GAC patients. MR: Military personnel are at higher risk for gastric cancer. This proposal will lead to novel target therapy and preventative strategies for high-risk GAC metastasis.	*Research not yet initiated*
CA170928 $574,768 Open	Fingleton/ Vanderbilt University	Advancing the Understanding of Lymphatic Metastasis in Colorectal and Gastric Cancers	RP: To test the hypothesis that implantation of GC or CRC cells into mesenteric lymphatic vessels is a robust model for lymphatic metastasis of CRC and GC that can be exploited for improving cancer care. MR: Military personnel are at greater risk for developing lymphoma due to exposure to cytotoxins and chemicals during deployment. This study will improve the understanding of lymphatic metastasis.	*Research not yet initiated*

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APPENDIX A: FISCAL YEAR 2012 (FY12)-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				
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: Multiple myeloma (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 Closed	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* *Employment: 1 (Assistant Professor)*
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* *Employment: 1 (Associate Professor)*
CA120128 $398,271 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* *Employment: 1 (Associate Professor)*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
BLOOD CANCER				
CA120184 $275,290 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)*
CA120212 $412,856 Closed	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.	*Presentations: 4* *Funding obtained: 1 grant* *Publications: 2* *Patent: 1* *Employment: 1 (Assistant Professor)*
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: 10* *Presentations: 19* *Funding obtained: 4* *Employment: 1 (PI promoted to Associate Professor)*
CA120381 $381,192 Pending Closeout	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.	*Publications: 6* *Funding obtained: 5 grants* *Presentations: 2*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
BLOOD CANCER				
CA130124 $362,154 Closed	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: 2* *Presentations: 3* *Funding Obtained: 1*
CA130155 $482,404 Closed	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*
CA130247 $534,407 Pending Closeout	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: 9* *Funding obtained: 1 grant*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
BLOOD CANCER				
CA130256 $364,538 Pending Closeout	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.	*Publications: 2* *Degree/Employment: Assistant Professor* *Funding Obtained: 5 grants* *Phase 1 trial of selinexor (KPT-330) in CLL and NHL*
CA130371 $270,365 Pending Closeout	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.	*None to date*
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.	*Publications: 4* *Presentations: 33* *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
COLORECTAL CANCER (CRC)				
CA120198 $374,403 Closed	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 U.S. military Veterans, as well as their families.	*Funding obtained: 2* *Publications: 2*
CA120206 $60,698 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 $359,317 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* *Employment: Associate Professor*
CA120296 $376,392 Closed	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 $417,338 Closed	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: 5* *Presentations: 1* *Employment: 1 (PI accepted a Group Leader position)*
CA120403 $373,200 Closed	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.	*Publications: 2* *Presentations: 5* *Patents: 3* *Funding obtained: 1 grant* *Employment: Research Associate*
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.	*Publications: 1* *Presentations: 1*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
COLORECTAL CANCER (CRC)				
CA150866 $91,144 Pending Closeout	Tackmann/ University of North Carolina-Chapel Hill	Characterizing the Role of Hep27 in Liver and Colorectal Cancer Stress Tolerance	RP: To characterize the role of Hep27 overexpression in colon cancer. The investigator hypothesized that Hep27 increases reactive oxygen species (ROS) tolerance, which contributes to therapeutic resistance. Using liver and colorectal cancer cell lines, this research suggested that Hep27 does not play a role in tolerance to oxidative stress. The investigator successfully defended her doctoral thesis and obtained new employment. 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.	*Degree Obtained: 1 (PhD)* *Employment Obtained: 1*
CA150873 $127,125 Pending Closeout	Sauer/ New York University School of Medicine	Structure and Function of the Reduced Folate Carrier	RP: This project aimed 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. Unfortunately, the 3D structure was not resolved due to technical issues but the PI obtained follow-on funding to perform the structural analysis of the proteins designed in this project using a new technique. 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.	*Funding Obtained: 1* *Publications: 2*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
GENETIC CANCER				
CA120215 $417,496 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*
CA140321 $528,000 Pending Closeout	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*
CA150794 $127,125 Pending Closeout	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.	*Presentations: 2* *Publications: 1*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
GENETIC CANCER				
CA150882 $125,694 Pending Closeout	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 (1) aim to broaden the currently rudimentary knowledge on how Ran and Ran binding proteins contribute to tumorigenesis and (2) will provide new opportunities to therapeutically target deregulated growth factor signaling in cancer. This 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.	*None to date*
KIDNEY CANCER				
CA120409 $370,143 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 (PI promoted from postdoctoral fellow to Assistant Professor)*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
KIDNEY CANCER				
CA130028 $474,562 Pending Closeout	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: Military personnel and Veterans have a higher rate of smoking and a higher rate of kidney cancer than does the non-military population.	*Funding Applied for: 1*
CA130458 $602,996 Pending Closeout	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: 6* *Presentations: 7* *Miscellaneous: 3*
CA140443 $340,501 Pending Closeout	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.	*Presentations: 3* *Funding Obtained: 1*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
LIVER CANCER				
CA150690 $115,500 Pending Closeout	Xu/ University of California, Los Angeles	Development of a Synthetic Lethal Drug Combination that Targets the Energy Generation Triangle for Liver Cancer Therapy	RP: This project aimed to examine the combinatorial effect of inhibiting multiple energy production pathways specific to hepatocellular carcinoma. By targeting the three main pathways of energy production, the researcher confirmed that the mono-targeted therapy or dual-targeted therapy could only slow tumor growth down. It was only with a tripartite approach that tumor cell death was induced. This work supports the idea that targeting these pathways together can facilitate tumor clearance beyond just slowing tumor growth. MR: Despite the increasing prevalence and lethality of HCC in the United States and among U.S. Veterans, there is a lack of effective and safe drugs available for clinical treatment.	*Presentations: 1*
CA150866 $91,144 Pending Closeout	Tackmann/ University of North Carolina at Chapel Hill	Characterizing the Role of Hep27 in Liver and Colorectal Cancer Stress Tolerance	RP: A project 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. After a year of investigation, the PI could not confirm a role for Hep27 in ROS accumulation. MR: The military population is particularly vulnerable to HCC given the higher rates of behavior and environmental exposures that are risk factors of this disease including HCV infection, obesity, diabetes, and alcohol abuse.	*Employment: Clinical Research Scientist, Impact Pharmaceutical Services (CRO)* *Degrees Obtained: PhD, UNC*
MELANOMA/SKIN CANCER				
CA120099 $400,800 Closed	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*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
MELANOMA/SKIN CANCER				
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* *Employment: Associate Professor, Mass General* *Funding obtained: 2 (R01 from NIDDK, R01 from NCI)*
CA120240 $399,600 Closed	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 may result from heavy sunlight exposure, an unavoidable circumstance 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: 3* *Presentations: 24* *Funding obtained: 2 (both from PRCRP)* *Employment: 1 (PI promoted to Associate Professor 1 July 2014)*
CA130184 $585,000 Closed	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*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
MELANOMA/SKIN CANCER				
CA130351 $550,800 Pending Closeout	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. In this project, the PI has mapped the molecular pathway of activity through which VISTA controls inflammatory response and identified which populations of immune cells are regulated by VISTA. Inhibition of VISTA signaling looks to synergize with T cell signaling in vivo to activate immune cells within the normally suppressive tumor microenvironment. 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.	*Presentations: 1* *Publications: 1*
CA130409 $464,034 Closed	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 Closed	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*
CA130537 $368,031 Pending Closeout	Khanna/ University of Connecticut Health Center, Farmington	Development of Cytomegalovirus-Based Vaccines against Melanoma	RP: The project developed and tested the efficacy of cytomegalovirus (CMV)-based anti-melanoma vaccines expressing single or multiple tumor antigens. In vivo experiments showed that tumor antigen expressing CMV can generate potent, long-lasting antitumor immunity due to recruitment of CD8+ and CD4+ T cells. This CMV based vaccine was able to protect mice from a highly metastatic form of melanoma, reducing tumor number and significantly slowing tumor growth in these mice. 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* *Employment: Associate Professor, NYU*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
MELANOMA/SKIN CANCER				
CA140744 $489,165 Pending Closeout	Fisher/ 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. When mice are treated with virus-loaded-MSCs in combination with anti-PD1 therapy, tumor growth and mouse survival are greatly affected and long-term survival observed in a subset of treated mice. MR: Melanoma is of particular interest to the military given that active duty personnel are often required to be outside for prolonged periods while stationed in sun-intense locales. Thus, military men and women face the potential for long-term risk of melanoma.	*Publications: 1* *Funding Obtained: 1* *Websites: 3*
CA150776 $131,250 Pending Closeout	Badrinath/ Dana-Farber Cancer Institute	Development of Epitope-Focused Tumor Vaccine to Prevent Escape from Immune Surveillance by the NKG2D Pathway	RP: Optimized a MICA alpha3 -based vaccine and validated its anti-tumor effect against subcutaneous melanomas and metastasis in mice. Tumor growth slowed and survival greatly increased in immunized mice challenged with MICA expressing tumors. 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.	*None to date*
CA150796 $124,874 Pending Closeout	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 activity or on its interactions with key transcription factors or co-activators. The findings from this study support the hypothesis that JARID1B acts through PGC-1α, a metabolic master regulator, to alter melanoma growth parameters. MR: Military Service members and Veterans face higher risk for melanoma and other skin cancers.	*Presentations: 1*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
MELANOMA/SKIN CANCER				
CA150818 $115,500 Pending Closeout	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.	*Publications: 1* *Funding Obtained: 1* *Miscellaneous: 1*
CA150852 $80,934 Pending Closeout	Barkauskas/ Queensland Institute of Medical Research	The Role of Adenosine A2BR in Metastatic Melanoma	RP: This project aimed to determine if adenosine 2B receptor (A2BR) played a critical role in melanoma metastasis by studying A2BR expression on the tumor cell surface and/or endothelium. No effect on tumor growth or metastasis was observed when A2BR was knocked out within the endothelium of melanoma bearing mice. 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.	*None to date*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
MELANOMA/SKIN CANCER				
CA150863 $100,757 Pending Closeout	Chang/ Memorial Sloan Kettering Cancer Center	A Therapeutic TCR Mimic Monoclonal Antibody for Intracellular PRAME Protein in Melanomas	RP: This project investigated the cellular mechanism by which the cancer specific peptide, PRAME(300-309), is presented on the surface of melanoma cells. The PI found that the immunoproteasome (IP) is more efficient than the constitutive proteasome (CP) at processing PRAME(300-309) and specifically the Beta5i subunit seems to be critical for PRAME(300-309) presentation. Additionally, an antibody which recognizes PRAME(300-309) was characterized and shown to bind the surface of melanoma cell lines. Unfortunately, this antibody did not show efficient binding within solid tumors, which greatly affects its utility as a potential melanoma therapeutic. However, the antibody was therapeutically active against non-solid tumors such as ALL and AML in vivo. 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.	*Publications: 1* *Presentations: 1*
CA150887 $112,525 Pending Closeout	Daenthanasanmak / Medical University of South Carolina	Tumor-Specific Th1/Th17 Hybrid Immunotherapy against Established Melanoma	RP: Characterized a novel cell type, hybrid Th1+/Th17+ T cells. Hybrid cells demonstrate superior function in tumor eradication compared to Th1 or Th17 cells. Hybrid cells persist long term and develop a memory phenotype that could mount tumor-specific immune responses upon second encounter. These cells also switch to produce interferon gamma as a mechanism to control tumor. These cells are long-lived and possess a stem cell like phenotype. 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.	*Publications: 1*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
MELANOMA/SKIN CANCER				
CA150892 $146,520 Pending Closeout	Li/ Sanford Burnham Prebys Medical Discovery Institute, La Jolla	Control of Immune Checkpoints by the Ubiquitin Ligase RNF5: Implications for Melanoma	RP: This study defined ubiquitin ligase RNF5 as a novel immune checkpoint in melanoma. Inhibiting RNF5 in mice attenuates melanoma cell growth and enhances tumor infiltration of T cells. This is the first study to identify a ubiquitin ligase as an immune check point, which enhances our understanding of how immune cells can be activated to target tumors. 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 after they leave the Service and would impact not only their health but also the emotional and financial well-being of their families.	*Presentations: 1* *Publications: 2 in revision*
CA150903 $117,855 Pending Closeout	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. PI found that HR ligands and TIL numbers are modified upon anti-CTLA4 therapy and the anti-tumor response to therapy correlates with increased HR ligand expression and TIL presence. These changes are dependent upon IFNγ signaling. 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 developing melanoma and/or other skin-associated cancers.	*Presentations: 1*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
MESOTHELIOMA				
CA120102 $254,373 Closed	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 fatal disease that can affect those exposed to asbestos.	*Publications: 1* *Presentations: 7*
CA120355 $360,000 Closed	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 promoted to Associate Professor)*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
MESOTHELIOMA				
CA130197 $379,039 Pending Closeout	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 and macrophages exposed to asbestos contain a unique proteomic signature, which may be responsible for their uptake by mesothelial cells. Application of these exosomes to mesothelial cells results in gene expression changes within the 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.	*Publications: 3* *Presentations: 2*
CA130248 $508,593 Closed	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 noninvasive 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* *Presentations: 2*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
MYELOPROLIFERATIVE DISORDERS				
CA140408 $453,875 Pending Closeout	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.	*Publications: 1* *Presentations: 3*
CA150767 $124,612 Pending Closeout	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 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.	*N/A*
NEUROBLASTOMA				
CA130153 $630,000 Pending Closeout	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 is determined in part by the health/welfare of their supportive families. Military missions benefit when Warfighters' families are healthy and well.	*Presentations: 5* *Publications: 1* *Miscellaneous: 1* *Funding Obtained: 1*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
NEUROBLASTOMA				
CA130396 $521,460 Pending Closeout	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 and pharmacodynamic measurements to predict drug response patterns in neuroblastoma (NB) tumors. The PI constructed the proposed PBPK model using two NB therapeutics and is testing the model's predictive capabilities. MR: The health and welfare of the force is determined in part by the health/welfare of their supportive families. Military missions benefit when Warfighters' families are healthy and well.	*Presentations: 4*
CA150807 $113,636 Pending Closeout	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.	*Publications: 1*
PANCREATIC CANCER				
CA120028 $405,600 Closed	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.	*Publications: 1*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
PANCREATIC CANCER				
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: 1* *Employment: Associate Physician, Mass General*
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-investigator on an NIH R01 from NCI)* *Employment: Assistant Professor, MD Anderson*
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.	*Publications: 3* *Presentations: 3* *Funding obtained: 2 (1 R33 from NCI)* *Employment: 2 (PI received tenure; promoted to Associate Professor)*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
PANCREATIC CANCER				
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*
CA130578 $566,796 Pending Closeout	Tuveson/ Cold Spring Harbor Laboratory	The Early Detection of Pancreatic Cancer in the U.S. 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: 3* *Funding obtained: 2 (R33 from NCI)*
CA140228 $531,685 Pending Closeout	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: 4* *Funding Obtained: 1 (F32 training grant)* *Computer Prog/ Software: 1* *Funding Applied for: 1* *Degrees Obtained: 1*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
PANCREATIC CANCER				
CA140634 $479,488 Pending Closeout	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.	*Publications: 1* *Miscellaneous: 2*
CA150842 $128,250 Pending Closeout	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 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.	*Publications: 2* *Presentations: 1*
PEDIATRIC BRAIN TUMOR				
CA120318 $400,425 Closed	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: 3* *Presentations: 2*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
PEDIATRIC BRAIN TUMOR				
CA130273 $522,410 Pending Closeout	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 is determined in part 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 Pending Closeout	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 is determined in part by the health and welfare of their supportive families. Military missions benefit when the Warfighters' families are healthy and well.	*Presentations: 1* *Funding Applied for: 3*
CA130436 $421,077 Pending Closeout	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 is determined in part by the health and welfare of their supportive families. Military missions benefit when Warfighters' families are healthy and well.	*Publications: 2* *Presentations: 14* *Funding Obtained: 1* *Publications: 5*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
PEDIATRIC BRAIN TUMOR				
CA130562 $169,472 Closed (Early Termination)	Mulcahy Levy/ University of Colorado at 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 is determined in part by the health and welfare of their supportive families. Military missions benefit when the Warfighters' families are healthy and well.	*None to date*
STOMACH CANCER				
CA150357 $196,971 Pending Closeout	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 U.S. Soldiers living under field conditions are at great risk of *H. pylori* infection, which is the main cause of gastric cancer.	*None to date*