UNDER SECRETARY OF DEFENSE
4000 DEFENSE PENTAGON
WASHINGTON, D.C. 20301-4000

PERSONNEL AND
READINESS

JAN 18 2016

The Honorable Kay Granger
Chairwoman
Subcommittee on Defense
Committee on Appropriations
U.S. House of Representatives
Washington, DC 20515

Dear Madam Chairwoman:

The enclosed report is in response to House Report 114-139, page 278, to accompany H.R. 2685, the Department of Defense Appropriations Bill, 2016 and Senate Report 114-63, page 201, to accompany S. 1558, the Department of Defense Appropriations Bill, 2016, concerning the Peer-Reviewed Cancer Research Program (PRCRP).

The fiscal year (FY) 2016 appropriation for PRCRP was $50M. The topic areas for FY 2016 were 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; and stomach cancer. A total of 90 projects were funded. The total amount of the FY 2016 PRCRP appropriation available for investment in research is $46.8M. This report includes a summary of all open and pending awards as of July 31, 2016, which includes the funding amount of the awards, progress of the research, and relevance of the research to Service members.

Thank you for your interest in the health and well-being of our Service members, veterans, and their families. A similar letter is being sent to the other congressional defense committees.

Sincerely,

Robert L. Wilkie

Robert L. Wilkie

Enclosure:
As stated

cc:
The Honorable Peter J. Visclosky
Ranking Member

UNDER SECRETARY OF DEFENSE
4000 DEFENSE PENTAGON
WASHINGTON, D.C. 20301-4000

PERSONNEL AND
READINESS

JAN 18 2018

The Honorable William M. "Mac" Thornberry
Chairman
Committee on Armed Services
U.S. House of Representatives
Washington, DC 20515

Dear Mr. Chairman:

The enclosed report is in response to House Report 114–139, page 278, to accompany H.R. 2685, the Department of Defense Appropriations Bill, 2016 and Senate Report 114–63, page 201, to accompany S. 1558, the Department of Defense Appropriations Bill, 2016, concerning the Peer-Reviewed Cancer Research Program (PRCRP).

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Sincerely,

Robert L. Wilkie

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Enclosure:
As stated

cc:
The Honorable Adam Smith
Ranking Member

UNDER SECRETARY OF DEFENSE
4000 DEFENSE PENTAGON
WASHINGTON, D.C. 20301-4000

PERSONNEL AND
READINESS

JAN 18 2018

The Honorable John McCain
Chairman
Committee on Armed Services
United States Senate
Washington, DC 20510

Dear Mr. Chairman:

The enclosed report is in response to House Report 114–139, page 278, to accompany H.R. 2685, the Department of Defense Appropriations Bill, 2016 and Senate Report 114–63, page 201, to accompany S. 1558, the Department of Defense Appropriations Bill, 2016, concerning the Peer-Reviewed Cancer Research Program (PRCRP).

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Sincerely,

Robert L. Wilkie

Robert L. Wilkie

Enclosure:
As stated

cc:
The Honorable Jack Reed
Ranking Member

UNDER SECRETARY OF DEFENSE
4000 DEFENSE PENTAGON
WASHINGTON, D.C. 20301-4000

PERSONNEL AND
READINESS

JAN 18 2018

The Honorable Thad Cochran
Chairman
Subcommittee on Defense
Committee on Appropriations
United States Senate
Washington, DC 20510

Dear Mr. Chairman:

The enclosed report is in response to House Report 114–139, page 278, to accompany H.R. 2685, the Department of Defense Appropriations Bill, 2016 and Senate Report 114–63, page 201, to accompany S. 1558, the Department of Defense Appropriations Bill, 2016, concerning the Peer-Reviewed Cancer Research Program (PRCRP).

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Sincerely,

Robert L. Wilkie

Enclosure:
As stated

cc:
The Honorable Richard J. Durbin
Vice Chairman

REPORT IN RESPONSE TO THE HOUSE REPORT 114-139, PAGE 278, TO ACCOMPANY H.R. 2685, THE DEPARTMENT OF DEFENSE APPROPRIATIONS BILL, 2016 AND SENATE REPORT 114–63, PAGES 201, TO ACCOMPANY S. 1558, The DEPARTMENT OF DEFENSE APPROPRIATIONS BILL, 2016

"PEER-REVIEWED CANCER RESEARCH PROGRAM"

SUBMITTED BY THE OFFICE OF THE ASSISTANT SECRETARY OF DEFENSE FOR HEALTH AFFAIRS

The estimated cost of this report or study for the Department of Defense (DoD) is approximately $8,360 in Fiscal Years 2016–2017. This includes $5,550 in expenses and $2,820 in DoD labor.
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PURPOSE

This report is in response to House Report 114–139, page 278, to accompany H.R. 2685, the Department of Defense (DoD) Appropriations Bill, 2016, and Senate Report 114–63, page 201, to accompany S. 1558, the DoD Appropriations Bill, 2016, that requests the Assistant Secretary of Defense for Health Affairs submit a report to the congressional defense committees on the status of the Peer-Reviewed Cancer Research Program (PRCRP). For each research area, the report should include the funding amount awarded, progress of research, and relevance to Service members and their families. This report provides the status of the fiscal year (FY) 2016 PRCRP, research accomplishments, and the relevance of PRCRP-supported research to Service members and their families. Table 1 provides PRCRP appropriation and topic area for FY 2016.

TABLE 1: PRCRP Appropriation and Topic Areas per Fiscal Year

Fiscal Year	Public Law	Appropriation	Topic Areas*	Awards‡
2016	114-113	$50M	Bladder cancer; Colorectal cancer; Immunotherapy; Kidney cancer; Listeria vaccine for cancer; Liver cancer; Lymphoma; Melanoma and other skin cancers; Mesothelioma; Myeloproliferative disorders; Neuroblastoma; Pancreatic cancer; Pediatric brain tumor; Stomach cancer	90†

*Topic areas are designated by Congressional language as published in the specified Public Law, Congressional Record, and post-Presidential signature communications for clarification on language.
†FY 2016 recommended awards were open for negotiation at the time of this writing and could change once negotiations are complete.
‡Number of awards represents all open, pending close-out, and closed awards; does not include withdrawals.

Over the years, the PRCRP has funded and managed numerous topic areas pursuant to Congressional guidance. Each FY, the investment portfolio is affected by many factors including: whether or not a topic area is present, the application receipt with respect to each topic area, the merit of the science and the impact of the proposed outcomes, and the appropriation amount with respect to the number of topic areas. The topic area of *Melanoma and Other Skin Cancers* has been continuously included under the PRCRP since the inception of the program. Other topic areas like *Bladder Cancer, Immunotherapy,* and *Lymphoma* were new to the PRCRP in FY 2016. Additionally, each topic area is considered during the programmatic review to ensure a balanced portfolio with respect to the specific FY topic areas. Total research recommended for funding by topic area for FY 2016 can be reviewed in Table 2.

TABLE 2: Total Research Dollars Invested per Topic Area for FY 2016

Topic Area	Total Dollars Recommended for Investment ($M)
Bladder cancer	5.4
Colorectal cancer	2.3
Immunotherapy	8.4
Kidney cancer	2.7
Listeria vaccine for cancer	0.6
Liver cancer	4.3

Topic Area	Total Dollars Recommended for Investment ($M)
Lymphoma	1.2
Melanoma and other skin cancers	5.4
Mesothelioma	2.7
Neuroblastoma	0.6
Pancreatic cancer	3.6
Pediatric brain tumors	4.0
Stomach cancer	6.1
Total Research Investment	**46.8**

CANCER RESEARCH RELEVANCE: SERVICE MEMBERS AND THEIR FAMILIES

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

The FY 2016 PRCRP sought to support studies that are responsive to at least one of the FY 2016 Military Relevance Focus Areas (Table 3).

TABLE 3: FY 2016 Military Relevance Focus Areas

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

In the first Military Relevance Focus Area, health risks associated with unique military environments were addressed. Service members, deployed across the world both in developed and developing nations, sustain environmental exposures that have been linked to the development of cancer. Several hazards have been identified that may play a role in the risk of carcinogenesis and the military population. Exposures linked to increased cancer risk include, but are not limited to, chemical weapons or storage, ionizing radiation, herbicides, electromagnetic fields, jet fuel, organic materials, biological agents, and ultraviolet radiation, among others (Table 4).

TABLE 4: Malignancies Associated with Military Service*

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

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

The PRCRP continues to fund meritorious research for the benefit of Service members and their families and to improve the quality of life for those impacted by a cancer diagnosis. A healthy family unit, free of serious illnesses, allows the Service member to focus on his or her role as a Warfighter and facilitates the overarching military mission. There are over 300,000 military beneficiaries with a cancer diagnosis, a prevalence of 4.1 percent, comprised of more than 60 different cancer types.[1] The cost of cancer care within the Military Health System (MHS) in FY 2002 was over $1 billion.[1] As shown by Lee et al., the MHS continues to diagnose and treat active duty Service members for a wide variety of cancers.[2] Funding studies on the detection, diagnosis, treatment, and prevention of these diseases benefits both the Warfighter and the American public, ultimately leading to increased survival rates and decreased costs of medical care.

SUMMARY OF RELEVANCE AND PROGRESS OF PRCRP AWARDS

Table 5 includes a summary of all open and pending awards as of July 31, 2016, in accordance with the Congressional language: "*For each research area, the report should include the funding amount awarded, the progress of the research, and the relevance of the research to Servicemembers*". The Department is committed to continued research in cancer to assist Service members and their families.

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

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

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

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

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

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

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

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

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

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Colorectal Cancer (CRC)				
CA140577 $310,000 Open	Gorham/ Naval Health Research Center	Serum 25-Hydroxyvitamin D and Subsequent Incidence of Colorectal Cancer in Active-Duty Personnel: A Nested Case-Control Study	RP: Study to quantify the relationship between 25-hydroxyvitamin D (25(OH)D) and incidence of CRC in active duty personnel. MR: This study will quantify prospectively the relationship between 25(OH)D in sera and CRC risk in active duty military, and provide information to indicate whether vitamin D may be useful in primary prevention of CRC. Primary prevention offers a further possibility of reducing incidence in the military.	*Publication: 1*
CA140616 $490,546 Open	Burnett-Hartman/ Kaiser Foundation Research Institute	The Association between Molecular Markers in Colorectal Sessile Serrated Polyps and Colorectal Cancer Risk	RP: A study to determine if there is a correlation between the histological characteristics of sessile serrated polyps (SSPs) and CRC risk in patients. Pathology review for 300 patient samples is underway and optimization of DNA methylation marker analysis is completed. MR: SSPs are associated with cigarette smoking, and cigarette smoking is associated with various cancers. Given that the prevalence of cigarette use in the military population is higher than in the general population, the utilization of SSPs as a new marker of CRC risk would be of greatest utility to the military population.	*Funding obtained: 3 grants*
CA140772 $466,500 Open	Messersmith/ University of Colorado Denver	Targeting the ALDH+ Tumorigenic Population in Colorectal Cancer	RP: This study will assess the effect of novel compound combinations that target WNT and NOTCH signaling pathways on tumor progression using patient-derived cells. Promising treatments will be validated against patient-derived xerographs. MR: CRC is the second leading cause of cancer death in the 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*

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

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

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

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

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

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

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Colorectal Cancer (CRC)				
CA161001 $247,500 Open	Mahara/ Monash University	Therapeutic Targeting of CIMP+ Colorectal Cancers	RP: This project will investigate whether small molecules that target the function of enzymes responsible for epigenetic modification can be used to rescue the function of previously inactivated tumor suppressor genes. Work on this project has just initiated. MR: Frequent exposure to cancer-associated agents places the US military population at higher risk for CRC.	*Research initiated*
Genetic Cancer				
CA100865/P1/P2 $1,085,960 Open	Alvarez; Couto; Huang/ Research Institute at Nationwide Children's Hospital; Ohio State University	Integrative Lifecourse and Genetic Analysis of Military Working Dogs	RP: Identification of environmental influences with potential to alter gene structure, stability, and expression, thereby altering cancer risk, and identification of specific genetic variations and environmental exposures, resulting in different epigenetic profiles capable of modifying cancer risk. The informatics infrastructure, statistical method for analyzing genetic data, and military dog registry database are established. Collection of blood samples and health records for the military working dogs has been initiated, and analysis is in progress. MR: The study of military working dogs, environmental exposures, and cancer risk will directly relate to military exposures and cancer risk within the human handlers population.	*Publications: 3* *Presentations: 7*

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

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

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

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Genetic Cancer				
CA150844 $80,370 Open	Wadugu/ Washington University	The Role of Mutant U2Af1 in the Pathogenesis of Myelodysplastic Syndromes	RP: The PI will create a novel mouse model of myelodysplastic syndrome (MDS) to determine if and how two mutations that often co-occur in the same tumor, U2AF1 and ASXL1, lead to tumorigenesis. MR: Identifying genetic mutations contributing to MDS initiation is key to developing effective prognostic and therapeutic strategies. The mouse models used here will be valuable reagents for the research community to test drugs in future preclinical studies.	*New research – no outcomes reported to date*
CA150882 $125,694 Open	Hsieh/ Cornell University Weill Medical College	Characterization of Ran Binding Protein (RANBP6) as Candidate Tumor Suppressor	RP: To test the hypothesis that the tumor suppressor function of ran binding protein 6 (RanBP6) stems from its role as regulator of nuclear import/export. The PI will identify RanBP6 substrates, characterize RanBP6 mutations that are common in multiple types of cancer, and explore the tumor suppressor activity of RanBP6 in a murine pancreatic organoid model. MR: These studies aim to broaden the currently rudimentary knowledge on how Ran and Ran binding proteins contribute to tumorigenesis and will provide new opportunities to therapeutically target deregulated growth factor signaling in cancer. 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.	*New research – no outcomes reported to date*

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

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Immunotherapy				
CA160356 $566,284 Open	Viapiano/ State University of New York Upstate Medical University	Engineering T Cells Against the Tumor Extracellular Matrix for Enhanced Immunotherapy of Mesothelioma	RP: Aims to determine whether Chimeric Antigen Receptor-expressing T cells targeted to the extracellular matrix of solid tumors could be used as effective therapy for malignant mesotheliomas (MM). The PI will engineer these new cytotoxic T cells and evaluate their specificity and efficacy in xenograft mouse models of mesothelioma. Work on this project has just initiated. MR: The major cause of MM is chronic exposure to asbestos, which was a common occurrence in 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.	*Research initiated*
CA160396 $612,000 Open	Gumperz/ University of Wisconsin at Madison	Modeling Human Gamma Delta T Cells as Antitumor Agents In Vivo	RP: Will determine what signals are required for a subset of poorly characterized T cells, the gamma-delta positive T cells, to control human lymphomas. Using engineered mice, the PI will administer gamma-delta positive T cells in the absence or presence of drugs that affect various aspects of T cell physiology and observe their influence on tumor burden in these mice. Work on this project has just initiated. MR: Exposure to militarily relevant chemical mutagens (e.g., Agent Orange) and ionizing radiation has been found to be associated with increased risk of developing B cell lymphomas. Novel treatments of this disease would therefore have a major impact on military personnel and their families.	*Research initiated*

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

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

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Immunotherapy				
CA161007 $236,627 Open	Pituch/ Northwestern University	Combination of IL13Ralpha2 CAR T-Cell Therapy with PD-1 Immune Checkpoint Blockade for Treatment of Glioblastoma	RP: Determine the central mechanisms (1) regulating CAR-T cell homeostasis at the glioblastoma multiforme (GBM) tumor site, (2) regulating infiltration into the GBM mass, and (3) of PD-1 mediated regulation of IL13Ra2-CAR T cell activity in immune competent mouse models of GBM. MR: GBM is an aggressive type of brain tumor; most people diagnosed are between the ages of 45 and 70, and the majority of those diagnosed are men, demographics that also strongly coincide with our Veteran population.	*Research initiated*
Kidney Cancer				
CA100606/P1 $1,206,215 Open	Tewari/ Fred Hutchinson Cancer Research Center Pantuck/ University of California, Los Angeles	Early Diagnosis of Clear Cell Kidney Cancer via VHL/HIF Pathway-Regulated Circulating microRNA	RP: Development of a serum miRNA-based biomarker for early detection of kidney cancer. Initially optimized the detection method for miR-210. Demonstrated that miR-210 was elevated in renal carcinoma serum samples. Identified seven additional miRNAs as potential serum biomarkers, which will be further examined along with miR-210. MR: Successful development of such a test will enable early cancer detection, removal at a curative and kidney-sparing stage, prompt recovery, and earlier return to active duty.	*Publication: 2*
CA120297 $364,353 Open	Krishnan/ University of North Carolina at Chapel Hill	Reprogramming of the Kinome to Enhance Mammalian Target of Rapamycin (mTOR) Inhibitor Responsiveness in Renal Cell Carcinoma	RP: To identify kinases upregulated by mammalian target of rapamycin (mTOR) inhibitors in renal cancer cell and determine if inhibition of these kinases improves the responsiveness of mTOR inhibitors in renal cell carcinoma. To date, the PI has found that the combination therapy of Dasatinib/Everolimus overcomes the acquired resistance to Everolimus alone in a PDX model of renal cell carcinoma (RCC). Additional studies explore the use of other kinase inhibitors to use in combination with Everolimus. MR: This study could potentially improve the outcomes and survival of military personnel with RCC.	*Publication: 1* *Presentation: 1* *Funding Obtained: 1*

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Mesothelioma				
CA130197 $391,875 Open	Shukla/ University of Vermont	Exosomes in Development and Therapy of Malignant Mesothelioma	RP: To study the role of exosomes, small lipid bound signaling packages, in the development and therapy of malignant mesothelioma to determine whether exosomes secreted from asbestos-exposed human lung macrophages and epithelial cells can transform human mesothelial cells. Initial research indicates that exosomes generated from epithelial cells exposed to asbestos contain a unique proteomic signature which may be responsible for their uptake by mesothelial cells. MR: Military and Veteran populations are at a higher risk of developing mesothelioma due to Service-related exposures to asbestos. Because of the long latency period of development of this cancer, cases will continue to appear in Veteran and military populations for decades to come.	*Publication: 1* *Presentations: 2*
CA140269 $400,613 Open	Najmunnisa/ University of Florida	Epha2 -/- NK Cell Therapy Against Malignant Pleural Mesothelioma	RP: This study aims to characterize the mechanism of tumor growth inhibition by natural killer (NK) cells lacking the EphA2 gene using a model of malignant pleural mesothelioma. The PI has confirmed that NK cells lacking EphA2 expression are more cytotoxic than wildtype cells. Targeting these NK cells to MPM cells show a significant reduction on tumor growth in co-culture systems. The in vivo activity of these MPM targeting NK cells will be tested in the second year of the project. MR: 30 percent of new cases of malignant pleural mesothelioma are reported in Veterans each year. Due to environment exposures including asbestos, Veterans are at a high risk of developing this fatal disease.	*Presentations: 1*
CA140385 $633,056 Open	Zauderer/ Memorial Sloan Kettering Cancer Center	BAP1 Mutations in Malignant Pleural Mesothelioma: Biology, Clinical Phenotypes, Radiotherapy Response, and Target Discovery for Somatic and Germline Mutations	RP: A study to understand the prevalence and association between mutations in the tumor suppressor gene BAP1 and clinical outcomes of mesothelioma. The PI has obtained biopsies from more than 100 individuals and is in the process of analyzing the prevalence of somatic and germline mutations within these patient samples. MR: Malignant mesothelioma disproportionately affects active duty Service members and Veterans due to their exposure to asbestos in the military.	*None*

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Stomach Cancer				
CA150357 $388,380 Open	Bao/ Brigham and Women's Hospital	Plasma Metabolomic Fingerprint of Early Gastric Cancer	RP: A study to describe the metabolomics fingerprint associated with gastric cancer. The 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.	*Research initiated*
CA150375 $607,557 Open	Reyes/ University of Texas Medical Branch Galveston	Molecular Characterization of *H. pylori* Strains and Biomarkers in Gastric Cancer	RP: This study aims to understand the genetic features of *Helicobacter pylori* strains linked to stomach cancer; and to identify biomarkers for stomach cancer. MR: Service members deployed to regions with higher *H. pylori* prevalence are at risk for *H. pylori* infection and stomach cancer. Stomach cancer is one of the top cancers treated in VA system.	*Research initiated*
CA150646/P1/P2 $2,081,946 Open	Janjigian; Lewis/ Memorial Sloan Kettering Cancer Center Tavazoie/ Rockefeller University	89Zr-Trastuzumab-PET, Rapid Autopsies, and Patient-Derived Xenografts to Determine the Extent of Clonal Evolution in Treatment-Refractory HER2+ Gastric Cancer	RP: This study aims to understand the mechanism of drug resistance in esophagogastric cancer (EG). The hypothesis is that HER2 levels between primary tumor and metastasis sites may contribute to the drug resistance. Furthermore, mutation of key kinases and deregulated expression of small non-coding RNAs (miRNAs) contribute to drug resistance in HER2-positive EG. MR: EG cancer is rapidly increasing and has high impact on the military and Veteran populations.	*Research initiated*

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

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

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

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

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