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

PERSONNEL AND
READINESS

JAN 28 2020

The Honorable James M. Inhofe
Chairman
Committee on Armed Services
United States Senate
Washington, DC 20510

Dear Mr. Chairman:

The enclosed report responds to House Report 115–219, pages 281–282, accompanying H.R. 3219, the Department of Defense Appropriations Bill, 2018, concerning the Peer-Reviewed Cancer Research Program (PRCRP).

The enclosed report summarizes the projects funded by the Fiscal Year (FY) 2018 PRCRP. The FY 2018 PRCRP funded 114 separate awards. Outcomes are expected by the end of the various awards performance periods, which span 2 to 4 years.

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,

Matthew P. Donovan
Performing the Duties of the Under Secretary of
Defense for Personnel and Readiness

Enclosure:
As stated

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

PERSONNEL AND
READINESS

The Honorable Adam Smith
Chairman
Committee on Armed Services
U.S. House of Representatives
Washington, DC 20515

JAN 28 2020

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PERSONNEL AND READINESS

JAN 28 2020

The Honorable Richard C. Shelby
Chairman
Subcommittee on Defense
Committee on Appropriations
United States Senate
Washington, DC 20510

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PERSONNEL AND
READINESS

The Honorable Peter J. Visclosky
Chairman
Subcommittee on Defense
Committee on Appropriations
U.S. House of Representatives
Washington, DC 20515

JAN 28 2020

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PERSONNEL AND READINESS

JAN 28 2020

The Honorable Jack Reed
Ranking Member
Committee on Armed Services
United States Senate
Washington, DC 20510

Dear Senator Reed:

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

PERSONNEL AND
READINESS

JAN 28 2020

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

Dear Representative Thornberry:

The enclosed report responds to House Report 115–219, pages 281–282, accompanying H.R. 3219, the Department of Defense Appropriations Bill, 2018, concerning the Peer-Reviewed Cancer Research Program (PRCRP).

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OFFICE OF THE UNDER SECRETARY OF DEFENSE
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PERSONNEL AND READINESS

JAN 28 2020

The Honorable Richard J. Durbin
Vice Chairman
Subcommittee on Defense
Committee on Appropriations
United States Senate
Washington, DC 20510

Dear Senator Durbin:

The enclosed report responds to House Report 115–219, pages 281–282, accompanying H.R. 3219, the Department of Defense Appropriations Bill, 2018, concerning the Peer-Reviewed Cancer Research Program (PRCRP).

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PERSONNEL AND READINESS

JAN 28 2020

The Honorable Ken Calvert
Ranking Member
Subcommittee on Defense
Committee on Appropriations
U.S. House of Representatives
Washington, DC 20515

Dear Representative Calvert:

The enclosed report responds to House Report 115–219, pages 281–282, accompanying H.R. 3219, the Department of Defense Appropriations Bill, 2018, concerning the Peer-Reviewed Cancer Research Program (PRCRP).

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Matthew P. Donovan
Performing the Duties of the Under Secretary of Defense for Personnel and Readiness

Enclosure:
As stated

REPORT TO CONGRESSIONAL DEFENSE COMMITTEES

CONGRESSIONALLY DIRECTED MEDICAL RESEARCH PROGRAMS

PEER REVIEWED CANCER RESEARCH PROGRAM

January 2020

The estimated cost of this report or study for the Department of Defense (DoD) is approximately $6,240 in Fiscal Years 2018-2019. This includes $3,520 in expenses and $2,720 in DoD labor.
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Peer Reviewed Cancer Research Program
Fiscal Year 2018 Report to Congress

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BACKGROUND AND PURPOSE OF REPORT

BACKGROUND

As directed by the Office of the Assistant Secretary of Defense for Health Affairs (OASD(HA)), the Defense Health Agency (DHA) J-9 (Research and Development Directorate) manages the Defense Health Program Research, Development, Test, and Evaluation appropriations, including funds for the Peer Reviewed Cancer Research Program (PRCRP). The U.S. Army Medical Research and Development Command Congressionally Directed Medical Research Programs (CDMRP) manages the PRCRP in support of OASD(HA) and DHA.

PURPOSE OF REPORT

This report is in response to House Report 115–219, pages 281–282, to accompany H.R. 3219, the Department of Defense (DoD) Appropriations Bill, 2018, which requests the Assistant Secretary of Defense for Health Affairs submit a report to the congressional defense committees on the status of the PRCRP. For each research area, the report should include the funding amount awarded, the progress of research, and its relevance to Service members and their families. This report provides a detailed update on the status of the Fiscal Year (FY) 2013–FY 2018 PRCRP awards, research accomplishments, and the relevance of PRCRP-supported research to Service members and their families. Assistance agreements (awards) have a period of performance of four years or less. The FY 2013–FY 2018 update provides information on awards actively monitored by the CDMRP. Previous updates for FY 2009–FY 2017 can be accessed at http://cdmrp.army.mil/prcrp/reports/reports.

FY 2009–FY 2018 PEER REVIEWED CANCER RESEARCH PROGRAM BACKGROUND AND OVERVIEW

From the PRCRP's inception in FY 2009 through FY 2018, congressional language has directed its appropriation amount and the different topic areas to be funded (Table 1). The majority of funds directed to the PRCRP are invested in research, while management and withhold costs are kept low. In FY 2018, 90 percent of the PRCRP appropriation ($80 million [M]) was allocated to research, while 10 percent was allocated to DoD withholds for Small Business Innovation Research and Small Business Technology Transfer, as well as execution management costs related to the PRCRP.

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

TABLE 1: PRCRP Appropriation and Topic Areas per Fiscal Year

Fiscal Year	Appropriation/ (Awards)‡	Topic Areas*
2009	$16M (38)	$4M, Melanoma and other skin cancers related to deployments of Service members to areas of high exposure; $2M, Pediatric brain tumors within the field of childhood cancer research; $8M, Genetic cancer and its relation to exposure to various environments that are unique to a military lifestyle; and $2M, Noninvasive cancer ablation treatment including selective targeting with nanoparticles
2010	$15M (30)	Melanoma and other skin cancers; Pediatric brain tumors within the field of childhood cancer research; Genetic cancer research and genomic medicine; Kidney cancer; Blood cancer; Colorectal cancer; *Listeria* vaccine for cancer; and Radiation protection utilizing nanotechnology
2011	$16M (44)	Melanoma and other skin cancers; Pediatric cancer research; Genetic cancer research; Kidney cancer; Blood cancer; Colorectal cancer; Pancreatic cancer; Mesothelioma; *Listeria* vaccine for cancer; and Radiation protection utilizing nanotechnology
2012	$12.8M (27)	Melanoma and other skin cancers; Pediatric brain tumors; Genetic cancer; Pancreatic cancer; Kidney cancer; Blood cancer; Colorectal cancer; Mesothelioma; and *Listeria* vaccine for cancer
2013	$15M (27)	Melanoma and other skin cancers; Pediatric brain tumors; Genetic cancer; Pancreatic cancer; Kidney cancer; Blood cancer; Colorectal cancer; Mesothelioma; and Neuroblastoma
2014	$25M (47)	Blood cancer; Colorectal cancer; Genetic cancer research; Kidney cancer; *Listeria* vaccine for cancer; Melanoma and other skin cancers; Mesothelioma; Myeloproliferative disorders; Neuroblastoma; Pancreatic cancer; Pediatric brain tumors; and Cancers related to radiation exposure
2015	$50M (110)	Colorectal cancer; Genetic cancer research; Kidney cancer; *Listeria* vaccine for cancer; Liver cancer; Melanoma and other skin cancers; Mesothelioma; Myeloproliferative disorders; Neuroblastoma; Pancreatic cancer; and Stomach cancer
2016	$50M (89)	Bladder cancer; Colorectal cancer; Immunotherapy; Kidney cancer; *Listeria* vaccine for cancer; Liver cancer; Lymphoma; Melanoma and other skin cancers; Mesothelioma; Myeloproliferative disorders; Neuroblastoma; Pancreatic cancer; Pediatric brain tumors; and Stomach cancer
2017	$60M (92)	Bladder cancer; Brain cancer; Cancer in children, adolescents, and young adults; Colorectal cancer; Immunotherapy; *Listeria*-based regimens for cancer; Liver cancer; Lymphoma; Melanoma and other skin cancers; Mesothelioma; Neuroblastoma; Pancreatic cancer; Pediatric brain tumors; and Stomach cancer
2018	$80M (114)†	Adrenal cancer; Bladder cancer; Blood cancers; Brain cancer; Cancer in children, adolescents, and young adults; Colorectal cancer; Immunotherapy; *Listeria*-based regimens for cancer; Liver cancer; Lymphoma; Melanoma and other skin cancers; Mesothelioma; Myeloma; Neuroblastoma; Pancreatic cancer; Pediatric brain tumors; and Stomach cancer

*Topic areas are designated by congressional language as published in the specified Public Law, Congressional Record, and post-Presidential signature communications for clarification on language.
†FY 2018 recommended awards under negotiation at the time of the writing of this report.
‡Number of awards represents all open, pending close-out, and closed awards, and does not include withdrawals.

In FY 2018, the PRCRP funded 99 applications[1] (representing 114 separate awards) of the 722 full applications received, for a 13.7 percent funding rate. For more information on the award selection process, access the Principal Investigator Information Paper (https://cdmrp.army.mil/

[1] Final applications awarded for funding are subject to change due to award negotiations. All FY 2018 award negotiations were completed by September 30, 2019.

prcrp/pdf/W81XWH-18-PRCRP-InformationPaper.pdf). All FY 2018 awards initiated research by September 30, 2019. Outcomes are expected by the end of each period of performance, which spans 2 to 4 years from the start date of an award.

Over the years, PRCRP funded and managed numerous topic areas as directed by Congress. Applications are evaluated using a two-tier review system, including peer review (i.e., assessment of the technical merit and impact) and programmatic review (i.e., comparison of each peer reviewed application with the portfolio composition and intent of the published program announcement). Figure 1 shows the percentage of dollars invested in each topic area from FY 2013−FY 2018. In each Fiscal Year, many factors affect the investment portfolio, including whether a topic area has been included; the number of applications received for each topic area; the scientific merit and impact of the proposed outcomes; and the appropriation amount with respect to the number of topic areas. Each topic area undergoes consideration during programmatic review to ensure a balanced portfolio with respect to the specific Fiscal Year topic areas. Table 2 shows total research recommended for funding by topic area for FY 2018.

FIGURE 1: FY 2013−FY 2018 PRCRP Research Investment per Topic Area (Percent of Total Research Dollars)

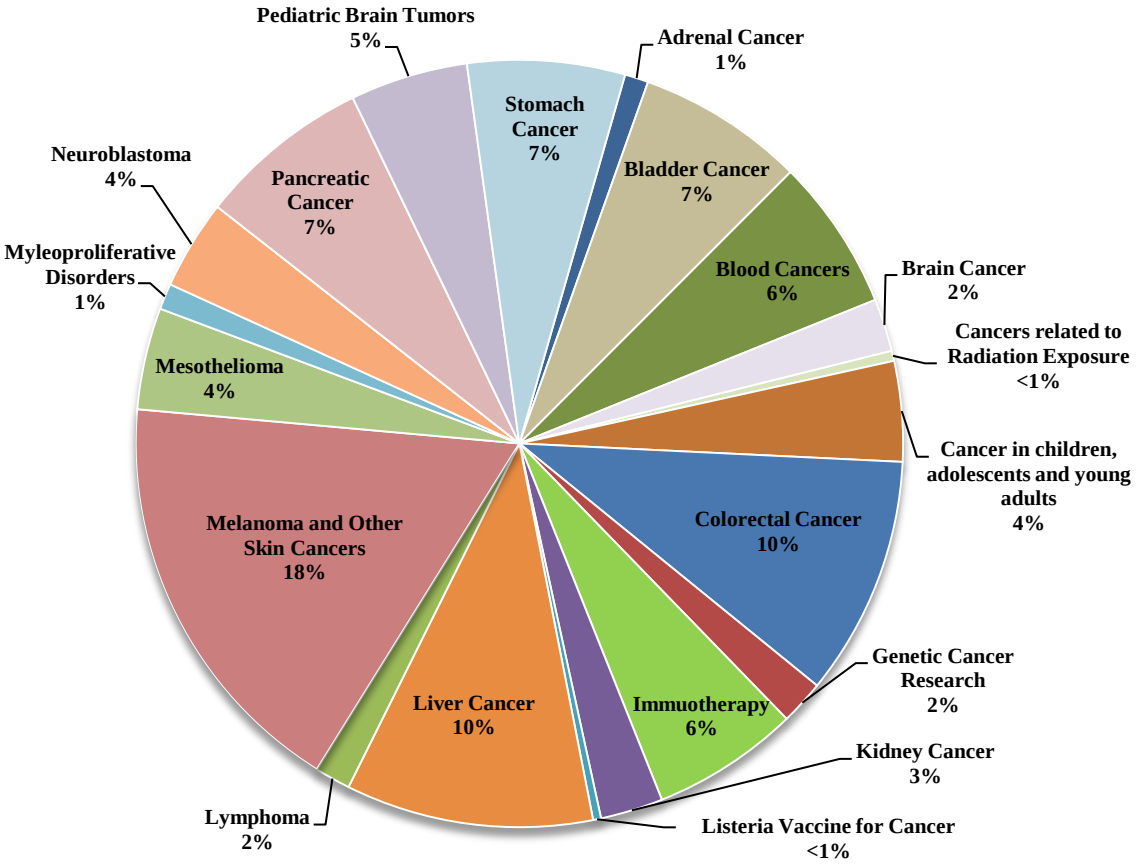

TABLE 2: Total Research Dollars Invested per Topic Area for FY 2018

Topic Area	Total Dollars Recommended for Investment ($M)*
Adrenal cancer	$2.2
Bladder cancer	$8.7
Blood cancers	$7.5
Brain cancer	$2.9
Cancer in children, adolescents, and young adults	$6.5
Colorectal cancer	$5.6
Immunotherapy	$6.7
***Listeria*-based regimens for cancer**	$0[]
Liver cancer	$7.5
Lymphoma	$1.0
Melanoma and other skin cancers	$8.3
Mesothelioma	$2.3
Myeloma	$2.2
Neuroblastoma	$1.5
Pancreatic cancer	$4.7
Pediatric brain tumors	$2.5
Stomach cancer	$1.5
Total Research Investment	**$72.9**

*Total Dollars Recommended for Investment have been updated from the initial information published in the Principal Investigator Information Paper (https://cdmrp.army.mil/prcrp/pdf/W81XWH-18-PRCRP-InformationPaper.pdf). The amounts in this table do not include applications recommended but withdrawn before negotiations could be finalized, but do include applications funded from the Alternate list with savings from award negotiations. FY 2018 recommended awards were under negotiation at the time of this writing. Total investment dollars were finalized by September 30, 2019.

[] No applications for the topic area were submitted for the FY 2018 PRCRP funding opportunities.

CANCER RESEARCH RELEVANCE: SERVICE MEMBERS AND THEIR FAMILIES

Congressional language has directed that research funded by the PRCRP should be relevant to Service members and their families. As a research funding program, the PRCRP crafts its investment strategy around the requirement to be relevant to military health concerns. All applications submitted to and funded by the PRCRP must show relevance to military health. The FY 2018 PRCRP addressed these core issues and relevance to military service by ***requiring*** that all applications address at least one of the FY 2018 PRCRP Military Relevance Focus Areas, as shown in Table 3.

TABLE 3: FY 2018 Military Relevance Focus Areas

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

ENVIRONMENTAL EXPOSURES

The PRCRP recognizes that military members may encounter hazards. Service members deployed worldwide, both in developed and developing nations, sustain environmental exposures linked to cancer risk. Multiple dangers have been identified that may play a role in the risk of carcinogenesis. Exposures linked to increased cancer risk include, but are not limited to, chemical weapons or storage, ionizing radiation, herbicides, electromagnetic fields, jet fuel, organic materials, biological agents, and ultraviolet radiation, among others (Table 4). Multiple sources, including the Department of Veterans Affairs (VA), have acknowledged that certain exposures increase the cancer risk of Service members and their families (Table 4).

TABLE 4: Malignancies Associated with Military Service

Topic Area	Military Gap	Relevance to Service Members, Their Families, and Veterans*
Adrenal Cancer	Exposure	Smoking rates in Service members
Bladder Cancer	Exposure	Fourth most common cancer among U.S. veteran population; incidence rate in veteran population is two times greater than that of the general population for exposures linked to pesticide containing arsenic.
Adult and Pediatric Brain Cancer	Exposure/ Readiness	Adult Brain Cancer: Occupational exposure link (especially electromagnetic fields). Pediatric Brain Tumor (PBT)/Neuroblastoma: In all childhood populations, PBT has the highest mortality rates of any childhood cancer; affects mission readiness.
Cancers in Children, Adolescents, Young Adults	Readiness	Cancers among support systems (e.g., family members) of Active Duty Service members affect mission readiness: 86 percent of the military are under the age of 39 (adolescents and young adults 15-39 years of age).
Gut Cancers (Colorectal, Liver, Pancreatic, Stomach Cancer)	Exposure/ Readiness	Colorectal Cancer: Active Duty screening decreases the mortality rates, but a 2008 report showed only 58 percent are up to date on screening; infectious diseases may be implicated. Liver Cancer: Veteran population has an increased hazard ratio: increased alcohol use leads to increased risk. Pancreatic Cancer: Direct link to environmental exposures (e.g., herbicides, smoking) may increase odds ratio among veterans. Stomach Cancer: Due to increased exposure to infectious agents [e.g., *Helicobacter pylori (H. pylori)*], veterans may have an increased risk.
Lymphoma/ Myeloma/ Blood Cancers	Exposure	Exposure to toxic chemicals/herbicides shown to increase risk; VA acknowledged association of Agent Orange and other herbicides with blood cancers in veterans. Exposure to ionizing radiation has shown a correlation with increased blood cancer risks.
Melanoma and Other Skin Cancers	Exposure/ Readiness	Studies have shown an increased risk of developing melanoma when exposed to high intensity solar radiation (with respect to area of deployment): increased risk compared to the Surveillance, Epidemiology, and End Results (SEER) data.
Mesothelioma	Exposure	Veterans account for more than 33 percent of all cases in the United States; exposure to asbestos is the leading cause.

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

MISSION READINESS

The second FY 2018 PRCRP Military Relevance Focus Area addresses gaps within the cancer care spectrum, which includes prevention, screening, early detection, treatment, and survivorship. Research that improves survival, while minimizing side effects, will have a major impact on mission readiness by enabling an Active Duty Service member to return to duty. Each Service member plays a crucial role in mission readiness. A Service member's cancer diagnosis affects not only the individual Soldier, Airman, Marine, or Sailor, but also every part of the unit and mission, decreasing mission readiness. Additionally, mission readiness extends to family members. Service members become affected when a member of their family, or support system, is in treatment for or receives a diagnosis of cancer. This may lead to a request for transfer, exceptional status, or even separation. A healthy family unit, free of serious illnesses, allows a Service member to focus on his or her role and facilitates the overarching military mission.

It is also important to note that the Military Health System (MHS) may cover military beneficiaries and veterans; thus, any improvements within the cancer care spectrum will also decrease the burden of health care on the overall MHS. There are more than 300,000 military beneficiaries with a cancer diagnosis, a prevalence of 4.1 percent, comprised of more than 60 different cancer types. In FY 2002, the cost of cancer care in the MHS was over $1 billion. The MHS continues to diagnose and treat Active Duty Service members for a wide variety of cancers. Addressing the key elements of cancer research and patient care is crucial to the mission of the PRCRP in relation to Service members, their families, veterans, and the American public. The PRCRP funds underrepresented and underfunded cancers for the health and welfare of the designated population. Investment in basic research lays the foundation for long-term applied and translational research, while funding more applied research areas shifts the field toward the ultimate goals: to advance mission readiness while increasing the quality of life for those affected by cancer. The impact of funding cancer research with respect to the military will reduce the burden of cancer on military families and improve force readiness. Furthermore, successful new studies will lead to innovative ways for preventing cancer development; improved diagnostic/detection methods; prognostic information; novel treatments; and better ways to cope with quality of life issues.

SUMMARY OF RELEVANCE AND PROGRESS OF PRCRP AWARDS

Table 5 includes a summary of FY 2013−FY 2018 awards as of July 31, 2019 (including awards under negotiation, open, and period of performance expiring). In accordance with the congressional language,[2] this report includes the log number, topic area, last name of the Principal Investigator (PI), award amount, institution, title, research progress, and military relevance for each funded award. Closed FY 2013−FY 2018 awards may be reviewed in Appendix A. For older awards (FY 2009−FY 2012), refer to the PRCRP website (http://cdmrp.army.mil/prcrp) and the CDMRP Search Awards site (http://cdmrp.army.mil/search.aspx) to review previous PRCRP Reports to Congress.

[2] "For each research area, the report should include the funding amount awarded, the progress of the research, and the relevance of the research to Service members."

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

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
ADRENAL CANCER				
CA180750 $616,736 Under Neg	Hammer/ University of Michigan, Ann Arbor	Intratumoral Steroid Production as a Mechanism of Immune Evasion in Adrenocortical Carcinoma (ACC)	RP: The PI hypothesizes that uncontrolled steroid production protects ACC from the immune system, preventing immune cells from penetrating the tumor. The PI will test the hypothesis that decreasing steroid production would increase the number of immune cells in ACC tumors, improving the response to immunotherapy. MR: ACC is a devastating and often fatal disease that affects Active Duty military, veterans, and their beneficiaries. ACC responds poorly to current treatments, which affects mission readiness and survivorship in military populations. This study will improve understanding of how steroid hormones affect ACC development and progression, and could improve current treatment options and outcomes for patients.	*Research not yet initiated*
CA180751/P1/P2 $1,556,422 Under Neg	Hammer/ University of Michigan, Ann Arbor Auchus/ University of Michigan, Ann Arbor Else/ University of Michigan, Ann Arbor	Biomarker Development for Diagnosis, Surveillance, and Prognosis for Adrenocortical Carcinoma (ACC)	RP: The three collaborating physician-scientist PIs on this award will assess whether steroid profiles can be used in the clinical management of ACC. They hypothesize that serum steroids can be used to diagnose ACC, measure ACC burden, and detect recurrence. MR: Military personnel are exposed to potentially cancer-causing agents while serving our country, including radiation during medical exams, which can lead to ACC formation. This research will evaluate whether previously identified biomarkers can be used to identify patients with ACC, and will assess risk of relapse.	*Research not yet initiated*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
BLADDER CANCER (BC)				
CA160108 $558,000 Open	Williams/ The University of Texas Medical Branch at Galveston	Agent Orange Exposure and Bladder Cancer	RP: The PI is data mining the VA Health system to determine whether there is a link between Agent Orange (AO) exposure, bladder cancer (BC) risk, and BC specific mortality. MR: If the aims of this proposal prove true, this information will be made available to all Service members, veterans, and their families who may be at increased risk for BC. Long-term outcomes may be improved by screening measures to identify patients sooner, when the disease is most curable. Furthermore, if the VA determines AO is a risk factor for BC, those exposed may have additional compensation and/or service-connected disability benefits.	*None to date*
CA160212 $610,199 Open	Faltas/ Cornell University, Weill Medical College	Dissecting the Role of APOBEC3 Mutagenic Proteins as Drivers of Genomic Instability and Chemotherapy Resistance in Urothelial Carcinoma	RP: The PI is testing the hypothesis that APOBEC3 proteins drive the development of chemotherapy-resistant urothelial carcinoma (UC) by mutating single-stranded deoxyribonucleic acid (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 relatively common risk factors among the veteran and Active Duty Service member populations, such as smoking and exposure to Agent Blue and industrial solvents (Institute of Medicine, 2014).	*None to date*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
BLADDER CANCER (BC)				
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 BC cells (CTC-PDX models) can be used to identify targetable mechanisms of cisplatin resistance. The PI is expanding and molecularly profiling this innovative model system platform, characterizing the DNA damage response mechanisms that contribute to cisplatin-resistance, and identifying novel therapeutic approaches. MR: BC represents the fourth most common type of cancer diagnosed in the VA Health System; tobacco use is the major risk factor. Recent studies indicate that Active Duty military personnel and veterans are more likely to smoke than the general U.S. adult population, and that military personnel who have deployed are more likely to smoke than those who have not deployed. Addressing sources of tobacco-related morbidity and mortality has clear and important implications for Service members, veterans, and their beneficiaries.	*None to date*
CA160312/P1/P2 $1,680,259 Open	Rosenberg/ Memorial Sloan Kettering Cancer Center McConkey/ Johns Hopkins University Van Allen/ Dana-Farber Cancer Institute	Precision Medicine in Platinum-Treated Lethal Bladder Cancer	RP: The three partnering PIs on this award are studying pretreatment samples collected as part of a Phase III trial of gemcitabine and cisplatin, plus bevacizumab or placebo, to determine (1) the association between DNA damage response and repair genes and clinical outcomes of the patients in this trial; (2) the impact of tumor subtypes on response to therapy; and (3) the underlying mechanism(s) that drive exceptional responses to treatment. The proposed correlative studies will be the largest genomic and transcriptomic analysis of metastatic BC conducted to date. MR: Military service remains one of the occupations associated with increased risk of BC, partly due to AO exposure and higher rates of BC-related mortality.	*None to date*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
BLADDER CANCER (BC)				
CA160487 $592,000 Open	You/ University of Oklahoma Health Sciences Center	Visible Light-Controlled Combination Strategy for Treating Non-Muscle Invasive Bladder Cancers	RP: The PI is testing the hypothesis that mitochondria-localizing and singlet oxygen (SO)-activated prodrug can be effectively activated by cancer cell-specific and mitochondria-specific PpIX (a photosensitizer formed in mitochondria) PDT, and thus greatly improve therapeutic efficacy with minimal collateral damage in the bladder. MR: BC is the fourth most common cancer among U.S. veterans due to several exposure risks: higher prevalence of smoking than in the civilian population, exposure to AO in Vietnam, and increased exposure to other industrial solvents like benzene.	*Publication: 1*
CA160685 $549,000 Open	Arora/ Washington University	Determinants of T-Cell Activity in Bladder Cancer	RP: The goal is to better understand the factors that influence BC immune surveillance and sensitivity to check-point blockade to extend the benefits of immune therapy to a greater number of BC patients and to maximize the response to therapy. MR: BC prevalence in military veterans is two times higher than in the general population. Through the studies proposed here, the PI will develop a better understanding of the barriers to immune rejection of BC, insights that will ultimately inform new strategies to treat members of the military and their families.	*None to date*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
BLADDER CANCER (BC)				
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 BC. Results to date indicate that SIMPHONY works by a combination of local ablation and the induction of systemic anti-tumor immunity. MR: Tobacco smoking is the most common etiology for BC, and military veterans have a higher incidence of smoking and developing smoking-related cancers. The second most common BC etiology is environmental carcinogens, and military personnel are at much higher risk for exposure to bladder carcinogens.	*Presentations: 3*
CA160934 $257,100 Open	Wardlaw/ Memorial Sloan Kettering Cancer Center	S-Phase Dynamics of the Mre11 Complex as a Barrier to Cancer	RP: In this study, the PI is (1) studying the S-phase specific roles of the Mre11 complex (typically associated with the DNA Damage Response) and how mutations observed in BC influence these roles; and (2) determining if this information can be exploited to develop therapeutic targets to treat BC. So far, the PI has found that in BC, many of the proteins whose replisome localization are altered commonly have genetic alterations. MR: As there is a higher prevalence of BC among veterans than the civilian population, any advance in understanding the disease mechanisms that leads to improved therapeutic options will improve the lives of those affected by BC.	*None to date*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
BLADDER CANCER (BC)				
CA170270/P1/P2 $1,527,574 Open	Meeks/ Northwestern University Svatek/ University of Texas Health Science Center at San Antonio McConkey/ Johns Hopkins University	Investigation of Genetic and Immune Mechanisms of Response to BCG for Non-Muscle Invasive Bladder Cancer: A Translational Study of S1602	RP: The goal of this project is to identify both the tumor-specific and immune-mediated responses that contribute to the tumoricidal effect of Bacillus Calmette-Guerin (BCG), leveraging samples collected from the Southwest Oncology Group 1602 (S1602) that included over 900 patients treated with BCG. MR: BC is the fourth most common cancer among veterans and develops secondary to smoking and exposure to environmental and deployment-related carcinogens. The successful completion of this project will have profound impact on the health and well-being of Active Duty Service members, veterans, and their beneficiaries.	*New Research – No outcomes reported to date*
CA170373 $615,026 Open	McGrath/ University of Rochester	Nanomembrane Capture and Characterization of Cancer-Derived Exosomes in Urine	RP: The PI will optimize methodology to efficiently capture exosomes (over 50 percent captured) from human urine samples and demonstrate the ability to distinguish exosomes derived from uroepithelial carcinoma from those that are not. MR: Recent findings have linked AO exposure to a statistically higher incidence of BC. The herbicide was used liberally to destroy jungle canopies in the Vietnam war and forests in the demilitarized zone (DMZ) during the Korean war.	*New Research – no outcomes reported to date*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
BLADDER CANCER (BC)				
CA170470 $608,000 Open	Lokeshwar/ Georgia Regents University	Development of Novel Noninvasive Tests for Prognostic Predictions for Bladder Cancer	RP: The main objectives of this proposal are to evaluate the efficacy of novel urine tests to (a) detect BC recurrence and early detection of muscle invasive BC, and (b) predict whether a patient will respond to Gemcitabine plus cisplatin neoadjuvant chemotherapy. MR: Smoking and chemical exposure are the major risk factors for BC. Compared to the general population, veterans and Active Duty Service members are twice as likely to be active or previous smokers. Additionally, recent evidence suggests a link between AO exposure and BC.	*New Research – no outcomes reported to date*
CA180175 $1,482,998 Under Neg	Theodorescu/ Cedars-Sinai Medical Center	Targeting the Regulation and Actions of Telomerase Reverse Transcriptase (TERT) in Bladder Cancer	RP: Telomerase Reverse Transcriptase (TERT) is a key component of telomerase, the complex that keeps chromosome ends from shortening and leading to cellular senescence. TERT overexpression is associated with cisplatin and doxorubicin resistance, and is observed in patients with a poor BC prognosis. The PI aims to identify and small molecule inhibitors that could reduce TERT expression, and develop drug combinations that will make the TERT-overexpressing cancer cells more vulnerable to therapy. MR: BC is the fourth most frequently diagnosed cancer among veterans, affecting 29,380 veterans from 1995 to 2008. While the BC death rate is dropping due to the advent of immunotherapy, approximately 70 percent of patients with invasive BC still die. Hence there is an urgent need for new effective therapies.	*Research not yet initiated*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
BLADDER CANCER (BC)				
CA180315 $616,000 Under Neg	Lee/ University of Rochester	Positive Loop of Smoking and Extracellular Vesicles in Bladder Field Cancerization	RP: The PI will test the hypothesis that, given the oncogenic properties of BC-derived extracellular vesicles (BCEVs) and cigarette smoking, and the positive regulation loop of smoke-induced stressful cellular environment and EV release, cigarette smoking induces BC cells to release oncogenic EV cargos and drive malignant transformation of normal urothelial recipient cells. The PI further expects that although the E-cigarette is less potent, it will still be able to promote tumorigenesis. MR: Studies have shown that U.S. veterans are twice as likely to be diagnosed with BC as the general population, and an increased incidence of smoking cigarettes in the military population may be a contributing factor. Thus, investigating the carcinogenicity of cigarette smoking in comparison to E-cigarettes and their interplay with BCEVs in an experimental model of "pre-malignant" bladder field is important.	*Research not yet initiated*
CA180495 $576,132 Under Neg	Meeks/ Northwestern University	Investigation of the Tumor Microenvironment as a Protective Niche That Supports Treatment Resistance of Bladder Cancer	RP: The PI will test the hypothesis that resistance to systemic therapy for patients with muscle-invasive BC is enhanced by development of protective niches in the tumor microenvironment that promote angiogenesis and restrict immune activity. The goal of this research is to identify the mechanisms of resistance and develop novel therapeutic strategies that may be combined with current therapeutic regimens. MR: BC is the fourth most common cancer among veterans and develops secondary to smoking and exposure to environmental and deployment-related carcinogens. Veterans with BC have higher rates of smoking (55 percent vs. 25 percent), exposure to AO (24 percent versus 21 percent), and/or chemical and biologic warfare (25 percent versus 11 percent) compared to those without BC.	*Research not yet initiated*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
BLADDER CANCER (BC)				
CA181008/P4 $1,694,463 Under Neg	Bhardwaj/ Icahn School of Medicine at Mount Sinai Sfakianos/ Icahn School of Medicine at Mount Sinai	Dissection of Suppressive Axes Underlying Natural Killer Cell Dysfunction in Human Bladder Cancer	RP: The PIs (Dr. Bhardwaj and Dr. Sfakianos) will use single-cell techniques to assemble high-resolution phenotypes of natural killer (NK) cell dysfunction and its evolution during non-muscle invasive and muscle invasive BC. They will then identify and develop approaches to restore NK function to enhance BC control. MR: U.S. veterans exposed to AO during their service in Vietnam may face an increased risk for BC. This proposal will accelerate advances in the detection, diagnosis, and treatment of BlCa and other solid tumors for the benefit of U.S. Service members.	*Research not yet initiated*
CA181011/P1 $1,563,127 Under Neg	Choi/ Johns Hopkins University Kim/ Prairie View A&M University	Development of Classifiers for Novel Bladder Cancer Subtypes	RP: The goal of this research is to obtain a better understanding of the biological significance and clinical implications of novel BC subtypes, and identify subtype-specific therapeutic targets using a pathway-guided, network-based algorithm on whole transcriptome data. The investigators will also optimize the number of subtype-specific biomarkers for clinical assay development. MR: BC is the fourth most common cancer among veterans, and is one of the more expensive cancers to treat. The development and implementation of novel BC sub-types to determine optimal therapeutic approaches could reduce the financial impact of treating veterans diagnosed with BC.	*Research not yet initiated*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
BLADDER CANCER (BC)				
CA181059 $706,000 Under Neg	Lam/ University of Washington	Precision Cotargeting Tumor and Its Microenvironment in Bladder Cancer	RP: The PI will test the hypothesis that the tumor microenvironment is instrumental in supporting BC cell survival at metastatic sites, and that precision co-targeting of the tumor and tumor microenvironment will maximally inhibit tumor progression. MR: The military population is at a disproportionally higher risk for BC and the diagnosis of aggressive BC negatively impacts mission readiness. Targeting metastases is historically difficult and ineffective using monotherapy. This project will provide a foundation for paradigm-shifting treatment from tumor-directed therapy to co-targeting a tumor and its microenvironment.	*Research not yet initiated*
CA181111 $633,600 Under Neg	Lee/ Fred Hutchinson Cancer Research Center	Multiplex Functional Interrogation of Oncogenic Networks in Bladder Cancer	RP: The objective of this project is to develop a rapid functional genomics approach using a mouse bladder urothelial model system to enable the multiplex interrogation of genetic aberrations and their contributions to the development of BC subtypes. MR: The major risk factors for BC are male sex, age, tobacco use, and chemical exposures. Military personnel were provided cigarettes in their rations until the mid-1970s, leading to increased rates of smoking, and also have the risk of being exposed to other carcinogens during the course of their service (i.e., inorganic arsenic in Agent Blue). Although genetic damage from tobacco use and chemical exposure is clearly linked to cancer development, the contributions of many genetic aberrations in BC are undetermined.	*Research not yet initiated*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
BLADDER CANCER (BC)				
CA181178 $658,800 Under Neg	Abbosh/ Institute for Cancer Research	Immunologic and Microbial Correlates and Mechanisms of Complete Response to Neoadjuvant Chemotherapy in Muscle-Invasive Bladder Cancer	RP: The PI's goal is to identify the immunologic and microbial correlates of pathological complete response of BC patients to neoadjuvant chemotherapy. MR: BC is more common among veterans than civilians due to carcinogenic occupational exposures and tobacco use. It is the most expensive cancer to treat, and bladder removal is a morbid and life-altering procedure. Therefore, improving muscle-invasive BC care for veterans is highly important.	*Research not yet initiated*
CA181350 $251,599 Under Neg	Antonelli/ Cornell University, Weill Medical College	Immunologic and Microbial Correlates and Mechanisms of Complete Response to Neoadjuvant Chemotherapy in Muscle-Invasive Bladder Cancer	RP: The PI aims to determine the mechanism by which BCG therapy induces and enhances a T cell-mediated tumor-specific immune response, and to shed new light on the anti-tumor immune signals that occur between T cells and tumor cells in BC. MR: This work will provide a more complete understanding of the mechanism of BCG therapy for BC, enabling improved patient outcomes, including improved outcomes for veterans.	*Research not yet initiated*
CA181410 $264,000 Under Neg	Jana/ Fred Hutchinson Cancer Research Center	Dissecting the Interface Between ARID1A and mRNA Translation in Bladder Cancer	RP: In this study, the PI will test the hypothesis that the translational capacity of bladder epithelial cells lacking the chromatin remodeler, ARID1A, may dictate the cells' ability to transform, and that this loss may serve as a therapeutic vulnerability in established cancers. MR: This work is particularly important for the progress of precision medicine because it seeks to mechanistically tie a significantly prevalent BC genotype (ARID1A loss) to a new therapeutic modality, which may significantly benefit veterans, Service members, and their families.	*Research not yet initiated*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
BLADDER CANCER (BC)				
CA181422 $257,700 Under Neg	Shah/ Health Research, Inc., Roswell Park Division	Studying the Effect of PPARG Pathway Modulation on Tumor Immune Microenvironment in Muscle Invasive Bladder Cancer	RP: In this study, the PI will test the hypothesis that inhibition of the nuclear receptor, peroxisome proliferator-activated receptor gamma (PPAR-gamma), blocks tumor progression by increasing CD8+ T-cell recruitment and M1 macrophage polarization. MR: According to the BC advocacy group, BCAN, military personnel are at a higher exposure to BC causing reagents. Thus, the identification of novel treatments for BC will directly benefit military personnel and the general public.	*Research not yet initiated*
BLOOD CANCER				
CA180214 $632,000 Open	Ji/ Northwestern University	The Role of Bone Marrow Inflammation in the Progression of Clonal Hematopoiesis to Blood Cancers	RP: In this study, the PI will test the hypothesis that inflammatory bone marrow microenvironment interacts with somatic mutations to promote Clonal hematopoiesis of indeterminate potential (CHIP) transformation to myelodysplastic syndrome (MDS). MR: CHIP is an important risk factor for the development of blood cancers in ageing veterans and their spouses. The study of the cooperative roles of somatic mutations in CHIP with the inflammation bone marrow environment is particularly important and disproportionately relevant in the military setting, due to the increased likelihood of inflammation in Active Duty Service members and veterans in comparison to the general population. Since Active Duty Service members and veterans have an increased chance of exposure to risk factors including infection and radiation, which are potent inducers of inflammation.	*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				
CA180252 $1,620,000 Open	Godley/ The University of Chicago	The Impact of Germline Predisposition to Myelodysplastic Syndrome on Allogeneic Hematopoietic Stem Cell Transplant Outcomes Using Related Donors	RP: In this study, the PI will seek to determine the frequency of germline mutations in MDS patients across the entire age spectrum, to associate the germline status of donor and recipient with engraftment kinetics and post-transplant outcomes. MR: Service members are at higher risk for blood cancer and MDS due to environmental exposures. The diagnosis of MDS will compromise the military readiness of Service members across the age spectrum.	*New research – no outcomes reported to date*
CA180334 $590,000 Open	Fisher-Wellman/ East Carolina University	Investigation into the Mechanisms of Acute Myeloid Leukemia (AML) Tumorigenesis and Chemoresistance via Systems Analysis of Mitochondrial Form and Function	RP: In this study, the PI will seek to (1) characterize the bioenergetics signature of AML tumorigenesis and chemoresistance; and (2) identify the mitochondrial protein kinases responsible for alterations in the mitochondrial phosphoproteome of AML mitochondria. MR: Environmental exposures, including chemical and ionizing radiation, are major risk factors for AML, which is considered a "presumptive disease" for veterans.	*New research – no outcomes reported to date*
CA180744 $618,000 Open	Perrotti/ University of Maryland, Baltimore	miRNA-Mediated Rescue of NK Cell Cytotoxicity Against Drug-Resistant Quiescent Leukemia Stem Cells	RP: In this study, the PI will test the hypothesis that bone marrow microenvironment induced lower numbers, and that dysfunctional NK cells significantly contribute to persistence of TKI-resistant quiescent chronic myelogenous leukemia (CML) leukemic stem cells through the induction of miR-300 and inhibition of miR-155. MR: CML and other myeloid malignancies (e.g., AML, MDS) occur at a higher incidence rate in Active Duty military personnel and veterans, and are associated with exposure during military service to hazardous mutagenic (e.g., ionizing radiation) environments. Thus, new therapeutic approaches aimed at eradicating myeloid leukemias at the stem cell level will benefit veterans.	*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				
CA180768 $641,827 Open	Adoro/ Case Western Reserve University	CHMP5 Dependency as a Posttranslational Vulnerability in T-Cell Leukemia	RP: In this study, the PI will test the hypothesis of post-translational stabilization of CHMP5 as a vital T-ALL dependency invoked by oncogenes. Targeted therapies that selectively disrupt CHMP expression and/or activity may represent a novel class of broad-acting T-ALL drugs. MR: Selective depletion of CHMP5 proteins can potently cripple T-ALL cells and alleviate the disease in many afflicted children and young adults, including military Service members and their families.	*New research – no outcomes reported to date*
CA181092 $1,614,999 Open	Mohi/ University of Virginia	Targeted Therapies for Myeloproliferative Neoplasms	RP: The objectives of this proposal are to determine the efficacy of a novel second-generation PIM kinase inhibitor TP-3654 and an allosteric SHP2 inhibitor SHP099, alone or in combination with JAK2 inhibitor Ruxolitinib, in pre-clinical models of myeloproliferative neoplasms/myelofibrosis (MPN/MF). MR: Military personnel are at increased risk of developing blood cancers, since herbicides (AO), chemical weapons, ionizing radiation, and environmental carcinogens have been linked to blood cancers including MPN. Successful completion of this project may lead to new therapeutic approaches for the treatment of MPN, and thus improve the health of U.S. military personnel, veterans, and their beneficiaries.	*New research – no outcomes reported to date*
CA181244 $593,996 Open	Zhang/ University of Southern California	Developing Novel Immunotherapeutics for Acute Myeloid Leukemia	RP: The goal of this study is to design and generate a series of synthetic multivalent antibodies retargeted exosomes (SMART-Exos) as artificial controllers of cellular immunity for better treatment of AML. MR: AML patients from the military are shown to have lower overall survival than that of civilians, which may be related to increased exposure to potential carcinogens and ionizing radiation. The proposed SMART-Exos as an innovative class of immunotherapeutics may provide new strategies for better treatment of military personnel with AML.	*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				
CA181323 $208,921 Open	Tang/ University of Minnesota Twin Cities	Targeting NF-kappaB-Inducing Kinase (NIK) for the Treatment of Hematologic Malignancies	RP: The goal of this study is to develop small molecule inhibitors of NIK as potential therapies for aggressive hematologic malignancies. MR: Veterans who participated in military service activities resulting in exposure to radiation and cancer-causing chemicals have a higher risk of developing hematologic cancers as they age. If successful, the results from this project will benefit those veterans who suffer from aggressive hematologic malignancies with activated NIK.	*New research – no outcomes reported to date*
CA181327 $107,226 Open	Whillock/ University of Iowa	Regulation of the B-Cell Receptor and B-Cell Homeostasis by Tumor Necrosis Factor Receptor-Associated Factor 3	RP: The goal of the study is to determine the role that TRAF3 plays in B Cell antigen receptor (BCR) signaling. The hypothesis is that TRAF3 restrains the BCR signaling pathway and effector functions by binding the BCR complex and recruiting inhibitory phosphatases. Thus, TRAF3-deficient B cells will be predisposed to aberrant cancer promoting elevated signals. MR: Service members are at risk for lymphoma due to increased environmental exposures. The knowledge derived from this project could lead to new targeted therapeutics for TRAF3-deficient B cell malignancies, and thus improve the lives of military Service members.	*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				
CA181397 $247,673 Open	Yusufova/ Cornell University, Weill Medical College	Linker Histone Mutations Mediate Lymphomagenesis Through a Novel Chromatin Mechanism	RP: The goal of this study is to test the hypothesis that H1 is required to maintain polycomb repressive complex 2 (PRC2) dependent silencing of a primitive stem cell program. The study's first aim is to determine the role and mechanism through which H1 is required to control the GC reaction. The second aim is to examine the molecular role and functional significance of linker histone mutations in B-cell lymphoma. MR: This project will yield substantial new information on the mechanism of action of H1; illuminate a novel role for H1 isoforms in regulating the humoral immune system; yield a new mechanism of disease pathogenesis previously unknown in lymphoma patients; and as such, directly benefit Active Duty Service members and veterans who are exposed to agents that lead to higher lymphoma incidence, as well as the general public.	*New research – no outcomes reported to date*
BRAIN CANCER				
CA170278 $602,000 Open	Noushmehr/ Henry Ford Health System	Epigenomic Master Regulators That Define IDH1/2 Mutant Glioma Tumor Progression	RP: The PI hypothesizes that glioma-CpG island methylator phenotype (G-CIMP)-high tumors relapse as G-CIMP-low gliomas, due to variations in DNA methylation and other epigenomic events, which then drive glioma progression. The PI will use next generation sequencing and insights into the relationship between transcription factor (TF), histone modifications, and DNA to investigate the functional genomic elements that define brain cancer progression between G-CIMP-high and G-CIMP-low. MR: Although environmental risk factors for glioma and glioblastoma remain poorly defined, with the exception of exposure to ionizing radiation, evidence has shown that traumatic brain injury may predispose Service members to gliomagenesis via inflammation and stem cell transformation.	*New Research – no outcomes reported to date*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
BRAIN CANCER				
CA170769 $508,129 Open	Warram/ University of Alabama at Birmingham	Dual PET/Fluorescence Imaging of Glioma with an MMP-14-Activatable Peptide Probe	RP: In this study, the PI will validate the concept of a matrix metalloproteinase 14 (MMP-14)-activatable probe for positron emission tomography (PET) with real-time surgical guidance via near-infrared fluorescence (NIRF) imaging of glioblastoma multiforme (GBM), and build the foundation to enable probe-guided resection of GBM in preclinical animal models, toxicology assessments, and, in future studies, trials in patients with GBM. MR: Exposure to ionizing radiation is the main external risk factor associated with GBM. Individuals, including military personnel exposed to nuclear weapons testing or other types of ionizing radiation, have increased risk compared to the general population of developing GBM.	*New Research – no outcomes reported to date*
CA170948 $624,000 Open	Van Meir/ Emory University	Role of N-Cadherin in the Therapeutic Resistance of Glioblastoma	RP: In this study, the PI will test the hypothesis that N-cadherin-mediated cell-cell adhesion induces adaptive resistance to radiotherapy in GBM by suppressing Wnt/β-cat signaling in glio stem-like cells (GSCs), resulting in a state of slow proliferation and stemness properties. Furthermore, the PI will test if therapeutic targeting of this process will prevent or reduce cancer cell resistance and augment patient survival. MR: If these studies support the use of N-cad pathway inhibitors as therapeutic radiosensitizers, these agents could be rapidly translated in GBM patients, since they are already approved for clinical trials. Success of this project will lead to the development of better therapies for the treatment of military personnel, their dependents, retirees, veterans, and the American public afflicted with GBM.	*New Research – no outcomes reported to date*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
BRAIN CANCER				
CA171074 $577,200 Open	Tiwari/ Case Western Reserve University	Systems Biology Approach to Predicting and Assessing Response to Chemoradiation for Brain Tumors	RP: The objectives of the proposed study are to develop and validate predictive EBI features for (a) identifying non-responders to chemoradiation therapy on pre-treatment MRI, and (b) distinguishing radiation necrosis from tumor recurrence on post-treatment MRI. MR: Brain tumor is a frequently occurring cancer in the veteran population; over 40 percent will develop a suspicious post-treatment lesion within a year after chemoradiation therapy. These patients could benefit from the clinically actionable tools developed in this project. Additionally, this proposal involves a collaboration with the Cleveland VA for independent validation of the tools. After successful validation of these tools, they will be embedded into the VA network to directly impact treatment management in brain tumors.	*New Research – no outcomes reported to date*
CA171145 $527,162 Open	Leavenworth/ University of Alabama at Birmingham	Boosting the Systemic and In Situ CD4+ T-Cell Responses to Malignant Glioma by Oncolytic HSV Virotherapy	RP: The goal of this project is to dissect the mechanisms of the antiglioma immune response that occurs as a result of treatment with the oncolytic virus, IL-12-oHSV. MR: Effective therapies represent unmet clinical needs for malignant glioma patients, including Gulf War veterans who are vulnerable to brain cancers. Results from the proposed study may form the foundation for future clinical approaches that benefit military personnel and the general population.	*New Research – no outcomes reported to date*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
BRAIN CANCER				
CA180174 $602,000 Under Neg	deCarvalho/ Henry Ford Health System	Targeting Oncogene Amplification in Glioblastoma	RP: The PI hypothesizes that inhibiting DNA-dependent protein kinase activity, and thereby DNA repair, will be effective in combination therapy regimens for glioblastoma. The goals of this project are to determine the efficacy of novel inhibitors targeting MDM2 and CDK4 in the treatment of glioblastoma. MR: Glioblastoma risk may be elevated by exposure to radiation, chemicals, and previous traumatic brain injury, which affects Active Duty Service members, veterans, and their families. Glioblastomas have a poor prognosis due to lack of effective treatment options, but results from this study could provide new therapeutic options that would benefit military personnel and the public.	*Research not yet initiated*
CA180344 $574,441 Under Neg	Cho/ Brigham and Women's Hospital	Developing Targeted Chemotherapeutics for Malignant Brain Tumors Using an Innovative "Blood-Brain Barrier Organoid" Platform	RP: High-grade gliomas, such as glioblastomas, are incurable, largely because current chemotherapeutics cannot pass the blood brain barrier (BBB) to reach tumor cells. The goal of this study is to develop a novel tumor-BBB platform to model how brain tumor cells interact with the BBB and respond to drug delivery. MR: Active Duty Service members and veterans are at increased risk of developing glioblastomas and other brain tumors due to chemical and radiation exposures and past traumatic brain injuries. Results from this study could lead to insight on how to deliver drugs more effectively to brain tumors, improving treatment outcomes.	*Research not yet initiated*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
BRAIN CANCER				
CA180386 $756,000 Under Neg	Verhaak/ Jackson Laboratory	Using Single-Cell Approaches to Determine the Mode of Disease Progression in IDH-Mutant Non-Codeleted Glioma	RP: Thirty percent of adult diffuse glioma patients have an IDH mutant non-codel subtype. Treatment options are limited, and the mechanisms for how these tumors progress are currently unknown. The goals of this study are to determine the pattern of tumor development in gliomas and the IDH mutant subtype, as well as identify which molecular signatures are associated with recurrence. MR: IDH-mutant non-codel gliomas have a median diagnosis age of 38 years, which directly affects Active Duty Service members and veterans. Results from this study could provide a new model to study gliomas that would allow more effective tracking of tumor growth, evolution, and recurrence, which is crucial for developing new treatment options.	*Research not yet initiated*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
BRAIN CANCER				
CA181256 $247,198 Under Neg	Krishnan/ Massachusetts General Hospital	Targeting the WNT Pathway to Reprogram the Tumor Microenvironment and Improve Immunotherapy of GBM	RP: Immune checkpoint blockers (ICBs) are a type of immunotherapy that has been effective in treating many types of cancer, but not glioslastoma multiforme (GBM). The PI hypothesizes that the GBM tumor microenvironment can be reprogrammed to be more sensitive to immune checkpoint blockers (ICBs). The goals of this study are to target two critical pathways in GBM that cause an immunosuppressive tumor microenvironment, and subsequently demonstrate improved efficacy of ICBs in a preclinical model. MR: There is a higher prevalence of glioblastomas among Active Duty Service members and veterans compared to the general population. Prognosis is very poor, due to the lack of effective treatments. Results from this study could provide new knowledge on how to reprogram the tumor microenvironment to make current treatment options, such as ICBs, more effective.	*Research not yet initiated*
CA181274 $264,750 Under Neg	Pal/ Dana-Farber Cancer Institute	Targeting the G2/M Checkpoint in Glioblastoma with a Combined Loss of TP53 and CDKN2A	RP: This study aims to evaluate whether G2/M checkpoint inhibitors can be an effective new therapeutic strategy for GBMs, as well as identify new biomarkers for CHK1/2 sensitive GBMs. MR: Glioblastomas affect Active Duty Service members, veterans, and their families, and lack effective treatment options. Results from this study could determine whether targeting the G2/M checkpoint would be a new therapeutic strategy for GBMs.	*Research not yet initiated*
CA181292 $240,041 Under Neg	Liu/ Duke University	Targeted Gold Nanoparticles (AuNPs) for Potent Alpha-Particle Radiotherapy of Brain Cancer	RP: The goal of this study is to develop a novel targeted alpha-particle radiotherapy using gold nanoparticles for brain cancer treatment. MR: There is an elevated risk of brain cancer in Active Duty Service members and veterans due to potential chemical and radiation exposure. The proposed study could provide a new targeted treatment option for brain tumors.	*Research not yet initiated*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
BRAIN CANCER				
CA181318 $241,619 Under Neg	Lee/ Massachusetts General Hospital	Targeting GABAergic Neuronal Signaling to Suppress IDH-Mutant Glioma Proliferation	RP: The PI hypothesizes that the IDH-mutant subtype of diffuse gliomas may express a type of GABA surface receptor that drives tumor growth. This study will evaluate whether these GABA receptors play a role in driving IDH-mutant glioma growth, and test whether altering the GABA signaling pathway can suppress growth. MR: The IDH-mutant subtype of gliomas typically affects younger adults between the ages of 20-45 years, the age group that also reflects a high percentage of Active Duty Service members and thus, directly impacts mission readiness. Results from this study could provide insight in the drivers of this tumor progression, and influence strategies to control tumor growth.	*Research not yet initiated*
CANCER IN CHILDREN, ADOLESCENTS, AND YOUNG ADULTS (CCAYA)				
CA170146 $622,000 Open	Jedlicka/ University of Colorado at Denver	Identification of Novel Epigenetic Modifiers of Metastasis Progression in Ewing Sarcoma	RP: This project employs an *in vivo* genomic screen to identify modifiers of the epigenome that are necessary for metastasis of Ewing Sarcoma (ES). MR: ES is an aggressive cancer of bones and soft tissues that disproportionately affects individuals within the age range eligible for active military Service.	*New Research – no outcomes reported to date*
CA170218 $615,578 Open	Modiano/ University of Minnesota Twin Cities	Mechanisms of Resistance to Immunotherapy in Osteosarcoma	RP: This study intends to describe the relationship between CD28, a receptor located on T cells, and resistance to immune checkpoint blockade in osteosarcoma mouse models. The PI will investigate the mechanisms by which micro-ribonucleic acid (RNA)s targeted to CD28 are released from osteosarcoma-derived exosomes as a way for the cancer to evade host immune response. MR: Osteosarcoma, a cancer that primarily affects children, adolescents, and young adults, has a slightly higher prevalence in military families than the general population, likely since 86 percent of Active Duty Service members fall within the adolescent and young adult age bracket.	*New Research – no outcomes reported to date*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
CANCER IN CHILDREN, ADOLESCENTS, AND YOUNG ADULTS (CCAYA)				
CA170273 $732,000 Open	Sykes/ Institute for Cancer Research	Targeting the Unfolded Protein Response in Pediatric Leukemia	RP: This study seeks to identify the transcriptional targets of ATF4 and XBP1S and assess chemical inhibitors in MLL-rearranged acute myeloid leukemia (AML). MR: Service members are at higher risk for leukemia due to chemical and radiation exposure. This study could potentially bring new therapeutics for AML.	*New Research – no outcomes reported to date*
CA170549 $641,000 Open	Kirsch/ Duke University	Modeling the Impact of Radiation Protectors on Radiation-Induced Sarcoma Risk	RP: This project aims to understand how sarcoma (i.e., cancer of muscles and connective tissue) develops following radiation exposure. The investigator believes that p53, a protein that protects cells from cancer, plays an important role. The study will use mice that do and do not express p53, exposing them to radiation and following the development of tumors. The study will provide insight into how radiation drives carcinogenesis. MR: Sarcoma is one of the most common childhood cancers. One major risk factor for developing sarcoma is exposure to radiation, either from radiotherapy for a different cancer type, or a radiological disaster like the Fukushima power plant meltdown in 2011.	*New Research – no outcomes reported to date*
CA171025 $662,124 Open	Halene/ Yale University	Mechanisms of Bone Marrow Failure and Leukemia Progression in Primary Human Fanconi Anemia Stem Cells in a Novel FA PDX Model	RP: This study intends to identify the causes and underlying mechanisms of oncogenesis in Fanconi Anemia (FA) using an FA PDX model. MR: Military beneficiaries are at higher risk of developing leukemia and cancer due to radiation and chemical exposure specifically related to war that may adversely interact with FA pathway mutations.	*New Research – no outcomes reported to date*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
CANCER IN CHILDREN, ADOLESCENTS, AND YOUNG ADULTS (CCAYA)				
CA180048 $452,605 Under Neg	Purdue/ National Cancer Institute	An Investigation of Serum Levels of Per- and Polyfluoroalkyl Substances and Testicular Cancer Risk Within the Department of Defense Serum Repository	RP: This project will investigate the link between exposure to chemical contaminants called polyfluoroalkyl substances (PFAS) and increased risk of testicular cancer in Active Duty military personnel. The investigator will utilize the DoD Serum Repository to analyze PFAS levels in Service members who developed testicular cancer. A second aim of this study is to determine if military bases with known PFAS contamination issues lead to elevated PFAS levels in Service members. MR: PFAS are a military-relevant risk factor associated with testicular cancer, as evidenced by DoD labelling these chemicals as emerging contaminants and conducting systematic testing for PFOA/PFOS in DoD water systems. Testicular cancer, the most commonly diagnosed cancer among U.S. Active Duty Service members, has high military relevance.	*Research not yet initiated*
CA180067/P1/P2 $1,539,441 Under Neg	Yeung/ University of Washington Pillarisetty/ University of Washington Gujral/ Fred Hutchinson Cancer Research Center	Novel Therapeutics for Fibrolamellar Carcinoma	RP: This study will investigate how a novel fusion protein, DNJA-PKAc, initiates liver tumorigenesis; identify the downstream signaling effects necessary to promote fibrolamellar carcinoma (FLC) growth; and determine how FLC evades the immune host response. MR: FLC typically affects young adults aged 15-35 years, which includes the age range of Active Duty Service members or young adults considering a military career. This work could lead to new mechanistic insights into how FLC develops, leading to new treatment options for this debilitating disease.	*Research not yet initiated*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
CANCER IN CHILDREN, ADOLESCENTS, AND YOUNG ADULTS (CCAYA)				
CA180741 $1,215,183 Under Neg	Stasko/ Novan, Inc.	Topical Nitric Oxide Therapy to Treat Cervical Neoplasias and Prevent HPV-Associated Cancers	RP: The goal of this research is to develop a self-administered nitric oxide-releasing vaginal suppository to treat cervical neoplasias, eliminate human papillomavirus (HPV) infection, and prevent progression to cancer. MR: Female Service members have an elevated prevalence of HPV infection compared to the general population, which is associated with development of cervical cancer. This study could provide a new way to treat cervical neoplasias and help prevent cervical cancer development.	*Research not yet initiated*
CA180783 $624,000 Under Neg	Porter/ Emory University	Development of Bispecific, T-Cell Engaging, Cytokine-Loaded Nanoparticles (BiTEokines) for the Treatment of Childhood Cancers	RP: The objective of this project is to improve chemotherapy for leukemia patients. The PI proposes to create nanoparticles that help immune cells engage with leukemia cells, while delivering the cytokine IL-12 to boost immune function. MR: Approximately 40 percent of Active Duty Service members have children, and this award addresses the most common cancer of childhood. Furthermore, over 80 percent of Active Duty personnel are adolescents or young adults, who have a much poorer prognosis with leukemia than children.	*Research not yet initiated*
CA181177 $220,350 Under Neg	Lawrence/ University of Texas Health Science Center at San Antonio	Transcription, R-Loops, and RNA Splicing in Ewing Sarcoma	RP: This project will assess the relationship between aberrant regulations of RNA processing in ES. Additionally, the investigator will evaluate the potential of targeting RNA processing mechanisms as a therapeutic target. MR: This research is relevant to military Service members and their families since ES disproportionately affects children and young adults, particularly male Caucasians.	*Research not yet initiated*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
CANCER IN CHILDREN, ADOLESCENTS, AND YOUNG ADULTS (CCAYA)				
CA181198 $633,993 Under Neg	Hong/ Dana-Farber Cancer Institute	Functional Interrogation of Nuclear Export Inhibition in SMARCB1-Deficient Cancers	RP: The PI will elucidate the mechanism by which nuclear export inhibition leads to cell death in multiple models of SMARCB1 deficient cancers. Then, the PI will assess if combining nuclear export inhibitors with proteasome inhibitors leads to increased therapeutic efficacy. MR: Whether Active Duty Service members or their children are involved, a cancer diagnosis is devastating. The proposed research focuses on a group of understudied cancers that occur in children and young adults who carry a poor prognosis, with the hopes of identifying new therapeutics that will extend and improve outcomes.	*Research not yet initiated*
CA181202 $155,000 Under Neg	Boehnke/ Massachusetts Institute of Technology	Leveraging Rational Nanoparticle Design for Improved Treatment of Pediatric and Adolescent Cancers	RP: This study's objective is to utilize a high-throughput pan-cancer screening approach (PRISM) to identify effective therapeutic NP formulations for the treatment of cancers found in children, adolescents, and young adults. MR: Based on the successful completion of this work, it is anticipated that many clinical collaborations will be initiated in order to pursue efforts of translating these NPs to the clinical setting to fill in gaps in cancer treatment that impact the health and well-being of military families and the general public.	*Research not yet initiated*
CA181215 $580,648 Under Neg	Murphy/ University of Texas Southwestern Medical Center at Dallas	Fertility and Reproductive Outcomes of Adolescent and Young Adult Cancer Survivors in Texas	RP: Adolescent and young adult cancer survivors are at risk of infertility due to cytotoxic chemotherapy and radiation treatments. This study's objective is to characterize fertility and reproductive outcomes and estimate risk of birth defects in this population. MR: Ninety percent of Active Duty Service members and their beneficiaries fall into the category of children, adolescents, and young adults. Rates of testicular cancer, thyroid cancer, and melanoma are higher among military members compared to the general U.S. population. Understanding fertility and reproductive health outcomes will directly affect Service members and their families.	*Research not yet initiated*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
CANCER IN CHILDREN, ADOLESCENTS, AND YOUNG ADULTS (CCAYA)				
CA181249 $264,750 Under Neg	Seong/ Dana-Farber Cancer Institute	Targeting Pediatric Fusion Oncoproteins via Protein Degradation	RP: This project aims to understand what regulates ES development. Characterization of the genetic mechanisms underlying ES will potentially lead to new targeted therapeutics to treat this cancer. MR: ES is the second most common bone cancer in children. Understanding the basic biology of ES will lead to improvements in the treatment of this disease and increase the quality of life in survivors, some of which are beneficiaries of Active Duty Service members.	*Research not yet initiated*
CA181344 $577,246 Under Neg	Chaudhury; Chakraborty/ Baylor College of Medicine	Therapeutic Targeting of Immune Dysfunction in Langerhans Cell Histiocytosis	RP: This project focuses on a myeloproliferative disorder called Langerhans cell histiocytosis (LCH). The investigator aims to develop pre-clinical models of LCH to determine the most effective therapeutic strategies for this disease. MR: LCH is about as common as pediatric Hodgkin lymphoma, but has poor clinical outcomes. This project will gain insight into this disease to improve long-term survival in patients, some of which may be military beneficiaries.	*Research not yet initiated*
CA181474 $264,375 Under Neg	Miranda-Roman/ Memorial Sloan Kettering Cancer Center	Overcoming Resistance to MEK Inhibitor Treatment in Malignant Peripheral Nerve Sheath Tumor (MPNST)	RP: The PI will test the hypothesis that malignant peripheral nerve sheath tumors (MPNSTs) become resistant to MEK inhibitor treatment due to increased expression of receptor tyrosine kinases (RTKs) over time, and subsequent activate the mitogen activated protein kinase (MAPK) signaling pathway. MR: MPNSTs not only affect young adults, but also can arise as a result of radiation therapy treatment for other cancer malignancies. Successful project completion will provide pre-clinical support for a combination therapy that could decrease mortality for thousands of MPNST patients. Therefore, this research will be of great benefit for both the military and general populations.	*Research not yet initiated*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
COLORECTAL CANCER (CRC)				
CA150370/P1/P2 $1,117,600 Open	Yeung; Pillarisetty/ University of Washington Tian/ Institute for Systems Biology	Tumor Slice Culture: A New Avatar in Personalized Oncology	RP: This study intends to establish a tissue-based platform to interrogate drug sensitivity and correlate the results with clinical and molecular data. This study will text cytotoxic chemotherapy, targeted kinase inhibitors, and immunotherapy will be tested on patient-derived tumor slice cultures of CRC liver metastases. In the first year of the award, the research team has begun to collect patient samples from the associated clinical trial and to initiate sensitivity assays on a small cohort. This project will examine the utility of this technique in future years, upon recruitment of an appropriate number of patients. MR: Military Service members incur exposures to various chemicals, biologics, and environments that are distinct from civilian exposures, which may result in cancer that exhibits distinctive biology or response to treatment. A personalized approach to treatment selection is therefore highly desirable.	*None to date*
CA150494 $534,985 Open	Wei/ University of Kentucky	Targeting Sulfiredoxin in Colorectal Cancer	RP: This study seeks to understand the mechanisms by which Sulfiredoxin (Srx), a protein that contributes to oxidative stress resistance, activates oncogenic signaling to promote CRC cell malignancy. This study will use cell culture experiments and mouse xenograft models 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 among veterans is very high and ranked as the third most commonly diagnosed cancer. Nearly 50 percent of patients initially diagnosed with CRC will develop distal metastases, and the five-year survival rate of patients with metastasis is only six percent.	*Presentations: 6* *Funding Obtained: 1*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
COLORECTAL CANCER (CRC)				
CA150582 $607,999 POPEX	Moriarity/ University of Minnesota Twin Cities	Targeted Therapy Combined with Immune Modulation Using Gold Nanoparticles for Treating Metastatic Colorectal Cancer	RP: This study aims to generate gold nanoparticles (AuNPs) to deliver a combinatorial therapy of immunogenic peptides and oncogene inhibitors systemically. The PI has had some success with the development of siRNA-conjugated gold particles. During the second year of the award, the study will assess the utility of the AuNPs *in vivo* using a mouse model of CRC. MR: Roughly five percent of all military personnel will develop CRC. Further, postulations exist that young military personnel, due to their exposure to infectious agents in foreign countries, may be at higher risk for developing gastrointestinal disease (e.g., irritable bowel disease, Crohn's disease, CRC) later in life.	*None to date*
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: This study seeks to develop novel computerized tools that utilize post-treatment MRI data to provide clinically actionable information about surgical treatment and its predicted benefit. In the first year, the PI utilized radiology and pathology data to map post-treatment changes spatially in rectal cancer patients. Initial results also indicate that non-invasive MRI data can be used to predict cancer phenotypes previously only determined by biopsy and/or resection. These characteristics include cancer stage, KRAS status, and response to treatment. Validation in larger patient cohorts from university hospitals and the Cleveland VA Medical Center will be performed in the coming years to determine the utility of these noninvasive prediction methods. MR: CRC is the third most frequently occurring cancer in the military, occurring in up to eight percent of veterans and five percent of Active Duty personnel. Over 75 percent of these patients will receive neoadjuvant chemoradiation therapy and would benefit from the tools developed in this project.	*Publications: 13* *Patent: 1* *Presentations: 12* *Website: 1*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
COLORECTAL CANCER (CRC)				
CA150908 $108,867 POPEX	Gomez/ University of Kansas Center for Research, Inc.	A Role for APC in Goblet Cell Function and the Unfolded Protein Response	RP: This project intends to determine the regulation, role, and function of the tumor suppressor Adenomatous Polyposis Coli (APC) in unfolded protein response (UPR) within colon cancer cells. The PI has observed colitis-induced patterning of both the APC protein and a marker of UPR within the colons of mice with chemically induced colitis. During the second year of the award, this study will further characterize these changes in human colitis tissue and other mouse models. MR: Approximately 10-15 percent of inflammatory bowel disease patients die from CRC. According to the American Cancer Society, an estimated 50,000 people will die from CRC in 2015. In the United States, CRC is the second leading cause of cancer-related deaths in men and women combined.	*Presentation: 1*
CA160344/P1 $802,575 Open	Frank/ Boston VA Research Institute, Inc. (BVARI) Lian/ Brigham and Women's Hospital	Targeting Therapeutic Resistance in Colorectal Cancer	RP: While promising new CRC therapies show improvement in patient survival, emergence of cancer resistance limits the long-term success of these treatments. This project will examine whether expression levels of known multidrug resistance mediator ABCB5 correlate with clinical outcomes among patients treated with CRC targeted therapies. Additionally, the research team will also investigate whether blocking ABCB5 can improve the longevity of these therapies in preclinical models. MR: CRC is a disease caused by exposure to ionizing radiation during military service. It is also one of the major causes of morbidity and mortality among military veterans. Thus, the identification and selective targeting of drug resistance mechanisms are of major importance for the long-term success of clinical disease treatments.	*New research – no outcomes reported to date*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
COLORECTAL CANCER (CRC)				
CA160741 $553,635 Open	Kim/ Yale University	Improving Immunotherapy: Boosting Immune Response and Functional Immune Cell Imaging	RP: This project aims to determine whether thermal ablation and immune checkpoint blockers can synergize their therapeutic effect when applied in combination within a mouse model of CRC. The PI will also develop novel imaging tools with potential to monitor immune response in real time using non-invasive techniques. MR: CRC is the third most common form of cancer among Active Duty personnel and veterans. Up to 50 percent of patients present with or develop distant metastases limiting the 5-year survival to 13 percent if unresectable. Thus, more effective treatment strategies are highly warranted to improve outcomes of patients with advanced CRC.	*New research – no outcomes reported to date*
CA160988 $192,966 Open	Malaby/ University of Vermont	Mechanisms of Selective Susceptibility to Inhibition of a Cytoskeletal Regulator in Colorectal Cancer Cells	RP: This project aims to characterize the effect of Kif18A depletion within multiple CRC cell lines. Kif18A is a motor protein associated with increased CRC metastasis and poor prognosis. MR: Statistics show that CRC is the second most deadly cancer for Service members.	*Presentations: 2*
CA161001 $247,500 Open	Mahara/ Monash University	Therapeutic Targeting of CIMP+ Colorectal Cancers	RP: This project will investigate whether small molecules that target the function of enzymes responsible for epigenetic modification can be used to rescue the function of previously inactivated tumor suppressor genes. MR: Frequent exposure to cancer-associated agents places the U.S. military population at higher risk for CRC.	*New research – no outcomes reported to date*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
COLORECTAL CANCER (CRC)				
CA170223/P1/P2 $1,599,817 Open	Waldman/ Thomas Jefferson University Weinberg/ Institute for Cancer Research Dominitz/ Seattle Institute for Biomedical and Clinical Research	Oral GUCY2C Ligand Blocks Colorectal Tumor Progression in Patients	RP: This project aims to determine whether treatment with the drug linaclotide to restore tumor suppressor GUCY2C signaling in CRC patients can repair the epithelial dysfunction observed in patients with adenomas or carcinomas. The research team will then use tissue collected from these patients to describe this drug's mechanism of action with greater precision. MR: The impact of CRC prevention strategies on the MHS can best be appreciated by considering that in 2015, medical care for new cases of CRC will cost the VA Health System about $400M annually, while the economic impact of each year of life lost is approximately $170M annually.	*New research – no outcomes reported to date*
CA170468 $616,850 Open	Linden/ Mayo Clinic and Foundation, Rochester	Feedforward Signaling Between Glia, Neurons, and Mast Cells Contributes to Polyp Formation and Growth	RP: This project seeks to determine signal mechanisms that contribute to increased innervation within the tumor microenvironment. The PI will examine the *in vivo* contribution of glia and neurons to polyp development and growth in mouse models of CRC. MR: This project has the potential to contribute to better understanding of the linkage between CNS dysfunction and oncogenesis, a major knowledge gap in the field of CRC.	*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)				
CA170613 $616,000 Open	Wong/ Oregon Health & Science University	Development of a Novel Circulating Tumor Cell Population for Early Detection of Recurrent Colorectal Cancer	RP: This study intends to investigate the function and relevance of circulating hybrid cells (CHCs), a fusion of macrophages and cancer cells, in colon cancer. It aims to determine whether CHCs can be a biomarker to track therapeutic response and disease in colon cancer patients. This study will include analyses of CHCs from colon cancer patients for gene expression profiles, followed by study of the CHCs, pre- and post-treatment, to determine whether treatment alters this population of cells, and whether detection of the cells predicts treatment response. MR: Colon cancer is one of the most common cancers, which will inevitably impact Service members, veterans, and their families.	*New research – no outcomes reported to date*
CA170670 $596,450 Open	Brock/ University of Texas at Austin	Targeting Resistance in Colorectal Cancer with a Novel Lineage-Tracking Technology	RP: This study intends to validate a novel fluorescent "DNA barcoding" method called BAASE that can track heterogeneous cell populations. This study will track CRC cells over time using BAASE to validate its efficiency in isolating specific populations. Then, these cells will undergo treatment with chemotherapeutics and monitoring to elucidate how drugs change the cell populations over time. Cells resistant to chemotherapy will be isolated for further characterization and tested for response to other drugs. MR: Chemoresistance is a major issue in the treatment of many cancers, including colon cancer. This award addresses gaps in cancer prognosis and treatment, which impact Service members, veterans, 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
COLORECTAL CANCER (CRC)				
CA170751 $634,000 Open	Gamero/ Temple University	The Role of the Gut Microbiome in Colorectal Cancer	RP: This project seeks to understand the genetic factors involved in shaping the intestinal microbial composition. The PI will investigate whether the microbiome of Stat2-deficient mice can be protective against both colitis and CRC. MR: Military personnel, either based in the United States or abroad, undergo exposure to a multitude of risk factors, including environmental, genetic, and dietary changes that are pathogenic in nature and may cause intestinal inflammation and changes to the structure of the gut microbiota.	*New research – no outcomes reported to date*
CA170922 $526,001 Open	Chen/ University of Michigan, Ann Arbor	Role of Noncoding Small RNAs in Colorectal Cancer Progression	RP: This project aims to investigate whether small non-coding RNA fragments are predictive of colon cancer development, and whether they impart an immune modulatory effect to promote tumor growth and maintenance. MR: Current CRC therapies extend overall patient survival by only two years on average, while CRC remains the third leading cause of cancer-related mortality.	*New research – no outcomes reported to date*
CA171000 $658,800 Open	Arora/ Institute for Cancer Research	Developing Biomarkers of Response to Chemoradiation Therapy in Rectal Carcinoma: Toward Precision Medicine	RP: This project aims to identify biomarker signatures for CRC patients who respond well to the current standard of care, neoadjuvant radiation therapy. The PI will compare both DNA and protein profiles of DNA damage, recognition, and repair pathways between patents with differing response to therapy to develop a dual component signature for therapeutic response prediction. MR: CRC incidence is increasing among young adults, a group of particular interest to the military.	*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)				
CA171019 $601,200 Open	Kelly/ Albert Einstein College of Medicine of Yeshiva University	Preventing Adverse Patient Responses to Cancer Chemotherapeutics	RP: This project aims to determine how the gut microbiome influences drug metabolism and contributes to adverse events in patients. The PI will attempt to correlate different metabolites of the anti-CRC drug CPT-11 to adverse events in patients, and examine which components of the gut microbiome are responsible for their generation. MR: CRC is a common cancer among Active Duty military personnel, and is the second leading cause of cancer-related deaths in the United States.	*New research – no outcomes reported to date*
CA171038 $626,832 Open	Ellis/ The University of Texas MD Anderson Cancer Center	Paracrine Role of Endothelial Cells in HER3-Mediated Colon Cancer Cell Survival	RP: This project seeks to identify the soluble factors secreted by liver endothelial cells that promote CRC survival. MR: Even though there are 10 U.S. Food and Drug Administration (FDA)-approved drugs for treating patients with metastatic CRC (mCRC), median survival of patients with mCRC is only about 2.5 years.	*New research – no outcomes reported to date*
CA171059 $615,240 Open	LaBarbera/ University of Colorado at Denver	Reversing EMT as a Strategy to Identify Effective Drug Combinations for Metastatic Colon Cancer	RP: This project intends to evaluate the antitumor potential of new combination therapies targeting epithelial-mesenchymal transition (EMT) in CRC using *in vitro* and *in vivo* techniques. MR: CRC is the third most prevalent type of cancer diagnosed with the second highest mortality rate, worldwide.	*New research – no outcomes reported to date*
CA171086 $623,668 Open	Shah/ University of Michigan, Ann Arbor	The Role of NF-kappa B2 Pathway in Colon Cancer	RP: This project will further define the role of NF-κB2 signaling in cancer cell proliferation and the maintenance of a pro-tumorigenic microenvironment. The PI will measure the recruitment and function of immune cells within the tumor microenvironment of NF-κB2 deficient mice and patient-derived colon tumors. MR: Colon cancer is one of the most common cancers among Active Duty personnel. Standard therapies are not beneficial for over 40 percent of patients at the time of diagnosis.	*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)				
CA171098 $636,000 Open	Hu/ Rutgers University	Chronic Stress and Its Effect on Cancer Therapy: Mechanism and Intervention	RP: This project aims to describe the signaling pathways involved in stress-induced chemo-resistance in mouse models of CRC. The PI will then examine whether targeting these pathways can enhance chemo-sensitivity in these same models. MR: This project investigates the effect of chronic stress on therapeutic response in CRC.	*New research – no outcomes reported to date*
CA171136 $618,120 Open	Ganesh/ Memorial Sloan Kettering Cancer Center	Investigating L1CAM-Dependent Stem Cell Regeneration in Colorectal Cancer Metastasis	RP: This project seeks to enhance understanding of the mechanisms required for CRC tumor initiation and metastasis. The PI will focus on proteins involved in maintaining intestinal epithelial integrity, and will examine *in vitro* and *in vivo* how disruption of cell-to-cell connections supports metastasis of CRC tumors. MR: CRC patients younger than 55 years of age are 58 percent more likely to be diagnosed with metastatic disease, which is usually incurable.	*New research – no outcomes reported to date*
CA171171 $542,982 Open	Lowe/ Texas Tech University Health Sciences Center, Lubbock	Immunotherapeutic Targeting of Colon Cancer Vascularization to Achieve Long-Term Immunity Against Primary and Metastatic Disease	RP: This project seeks to investigate and characterize a new therapeutic vaccine strategy against CRC. The PI will examine the acute therapeutic effect of these vaccines in tumor-bearing mice, and observe whether treated mice maintain long term immunity. MR: CRC is the third most common diagnosed cancer in the United States, and afflicts the specific age groups of Active Duty military personnel.	*New research – no outcomes reported to date*
CA180365 $1,571,597 Under Neg	Maker/ University of Illinois at Chicago	Enhancing Immunotherapy with Novel Combinations to Improve the Treatment of Primary and Metastatic Colon Cancer	RP: This study aims to stimulate the immune system to increase the infiltration and activation of anti-tumor lymphocytes in colon cancer tumors and metastases. MR: Active Duty Service members and veterans may be at increased risk for developing CRC due to infections and previous exposures. This research could provide new immunotherapy treatment strategies for colon cancer.	*Research not yet initiated*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
COLORECTAL CANCER (CRC)				
CA180748 $674,000 Under Neg	Gala/ Massachusetts General Hospital	Precision Approaches to Early-Onset Colorectal Cancer Therapy Through Germline Variation	RP: The PI hypothesizes that certain DNA damage repair pathways are enhanced in individuals with early-onset CRC, and this could make tumors more sensitive to precision chemotherapeutics. This study will identify germline mutations in DNA damage repair pathways associated with CRC and identify tumor response to precision chemotherapeutics. MR: Military personnel are exposed to colorectal carcinogens such as solvents and radiation, and CRC is on the rise among young adults that make up a large percentage of Active Duty Service members. Results from this study will provide insight on how mutations in DNA repair genes impact colorectal tumor development, and resulting mutational signatures could help identify at-risk individuals.	*Research not yet initiated*
CA180837 $568,487 Under Neg	Gruev/ University of Illinois at Urbana-Champaign	Bioinspired Color and Near-Infrared Endoscopy with Affibody Targeted Markers for Colorectal Cancer Surgery	RP: This project will develop an imaging sensor to work in concert with tumor-targeted probes to better detect flat lesions and small polyps during colonoscopy screenings. MR: CRC is a large threat to military veterans, as well as their family members, with approximately 3,500 VA patients diagnosed each year. Earlier detection and more advanced screening methods are crucial to combat this disease. This study could provide a superior imaging system for routine colonoscopies to identify and detect lesions and polyps, which could reduce mortality rates.	*Research not yet initiated*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
COLORECTAL CANCER (CRC)				
CA180925 $586,000 Under Neg	Buckhaults/ University of South Carolina	TP53 Synthetic Lethal Screen in Organoid Avatars to Discover Novel Therapeutic Targets for Colon Cancer	RP: TP53 mutations are common in colon cancers and often lead to chemotherapy resistance. This study will screen human colon cancer organoids for TP53 mutations, identify novel gene knockouts that can re-sensitize TP53-mutated colorectal tumors to chemotherapy, and identify novel combination therapies to effectively target TP53 mutant cells. MR: Colon cancer affects Active Duty military personnel, veterans, and their beneficiaries. TP53 mutations are found in 50 percent of these tumors, which eventually become resistant to chemotherapy and thus, impact mission readiness. Results from this study may produce new targets for the treatment of TP53 mutant colon cancer, as well as identify novel combination therapies for TP53-mutated colon cancer.	*Research not yet initiated*
CA181043 $544,215 Under Neg	Bhattacharya/ The University of Texas MD Anderson Cancer Center	Identification and Validation of Novel Combination Therapies for KRAS-Mutated Colorectal Cancer Using Unbiased and Innovative Screening Strategies	RP: Over 50 percent of patients with CRC have a mutation in the oncogenic driver KRAS, so there are a number of drugs on the market that target KRAS and its mediators. However, these drugs have shown limited efficacy as standalone therapies. This study will screen these currently available drugs to identify combinations that could work together to enhance cell death in CRC cells with KRAS mutations, and will perform preclinical studies in mice models to demonstrate efficacy. MR: CRC is the fourth most common cancer in military personnel, and poses a threat to mission readiness. Results from this study could identify novel drug combinations that would improve treatment of this disease.	*Research not yet initiated*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
COLORECTAL CANCER (CRC)				
CA181126 $568,800 Under Neg	Houghton/ Vanderbilt University Medical Center	Development of a Novel Platform for *In Vivo* Delivery of Antagomirs to Study Cetuximab Resistance in Colorectal Cancer	RP: This study will develop a platform for delivery of modified RNAs (miR-100 and miR-125b) to CRC cells, and monitor their ability to target cetuximab-resitant CRC cells. MR: CRC is the third most commonly diagnosed cancer in the VA population and has a poor prognosis, pointing to a need for new and improved therapies. This proposed work could yield a new platform for drug delivery to cancer cells that have become resistant to current chemotherapeutics.	*Research not yet initiated*
CA181267 $235,500 Under Neg	Daron-Mathis/ Vanderbilt University	Anticancer Efficacy of CBD Pure Isolates and Commercially Available Water-Soluble CBD in Colorectal Cancer	RP: This study will investigate the pharmacokinetic effects of cannabidiol (CBD), and whether CBD has anti-tumor effects that could be used to treat colorectal tumors. MR: CRC impacts Active Duty Service members and their beneficiaries, and has high prevalence among veterans. Results from this study could help identify whether commercially available CBD has anti-tumor effects and outline the safety and efficacy of this compound for future treatments.	*Research not yet initiated*
CA181446 $241,500 Under Neg	Navickas/ University of California, San Francisco	Characterization and Therapeutic Targeting of a Novel Metastasis-Suppressive Pathway in Colon Cancer	RP: This study will characterize the mechanisms by which RNA-binding protein 1 (RBMS1) functions in colon cancer cells, and investigate ways to reactivate RBMS1 to reduce metastatic spread. MR: CRC is highly prevalent among veterans and military personnel. Results from this study could provide insight on whether the RBMS1 pathway plays a role in suppressing metastatic progression of CRC, which could lead to a novel therapeutic drug target.	*Research not yet initiated*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
COLORECTAL CANCER (CRC)				
CA181455 $576,000 Under Neg	Sahni/ The University of Texas MD Anderson Cancer Center	Novel Systems Biology Approach to Decoding Actionable Targets to Overcome Resistance in GI Cancer Monotherapies	RP: This study will look to discover new drug targets to overcome resistance in gastrointestinal (GI) cancers, specifically CRC; test drug combinations and characterize their effects against monotherapy-resistant GI cancers; and identify the mechanisms for drug resistance in GI cancers. MR: Military members and veterans are susceptible to GI cancer development such as CRC, due to exposures to infection, radiation, and irregular diets. Results from this study could identify new combination therapeutic strategies to treat GI cancers.	*Research not yet initiated*
GENETIC CANCER				
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: The PI has evidence that antagonists of the protein MDM2 could be used to selectively eliminate mutant clones in myelodysplastic syndrome arising from radiation or chemical exposure. As there are several MDM2 antagonists under clinical development, results from this study have the potential for rapid clinical translation. 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.	*Presentation: 1*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
GENETIC CANCER				
CA150414 $606,975 POP Exp	Magnuson/ University of North Carolina at Chapel Hill	Co-Occurrent Mutations in Chromatin Regulators Define Genetically Distinct Forms of Cancer	RP: The PI has created tools to help prioritize mutations commonly found in hepatocellular carcinoma (HCC). The PI will 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 are 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 to 1965. The high mortality rate associated with liver cancer makes linking the mutations of the disease to new therapeutic targets a pressing need for this population.	*None to date*
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 seeks to improve methods of chimeric antigen receptor (CAR) T-cell immunotherapy. The investigator's novel method involves the use of T-cell targeted ultrasound mediated gene transfection using "microbubbles" that contain the targeted gene of interest. This method will allow clinicians to deliver CAR-T directly, rather than through the current lengthy method. In the first year, the investigator has demonstrated cultured T cells can be transfected with the microbubbles. The composition of the microbubbles is undergoing further optimization before initiation of *in vivo* animal testing. MR: Childhood malignancies are devastating to families who watch their child suffer and potentially succumb to this disease. It also creates stress and financial and time costs on caregivers, especially if a parent is an Active Duty Service member with time commitments away from home.	*None to date*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
IMMUNOTHERAPY				
CA160218 $399,723 Open	Zhao/ University of California, Irvine	Context-Dependent CAR Activation: Engineering Mechanosensitive T Cells to Treat Solid Tumor Metastases	RP: This project aims to improve CAR-T cell therapy by creating CAR-T cells that activate only in the presence of specific tumor microenvironment signals. The PI is working to identify transcription factors used by the T cell to recognize unique mechanical properties of solid tumors. Once these factors have been identified, the optimized CAR-T will be tested using *in vivo* animal models of metastatic CRC. MR: Developing new CAR-T cell therapy to treat metastatic CRC will potentially benefit military beneficiaries, as the CRC incidence rate is skewed toward current veterans due to age- and exposure-related risks.	*New research – no outcomes reported to date*
CA160315 $568,800 Open	Luke/ The University of Chicago	Genomic and Commensal Variants Associated with Immunotherapy in Cancer Patients	RP: The goal of this project is to identify factors that suppress immune cell infiltration into tumors. The Cancer Genome Atlas (TCGA) and patient samples are being used to identify signaling pathways, genetic mutations, and microbiota differences that correlate with immune suppression in the tumor microenvironment, response to therapy, and clinical outcomes. In the first year of the project, the PI observed an inverse correlation between WNT/beta catenin signaling components and inflammatory tumors. These data suggest the need to develop pharmacologic inhibitors of beta catenin to promote immune cell infiltration into the tumor and improve immunotherapy regimens. 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.	*Presentation: 1* *Publication: 1* *Clinical Trial: 1*

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: This project is studying CAR-T cells targeted to the extracellular matrix of solid tumors in the treatment of malignant mesotheliomas (MM). In the first year of the award, the PI successfully engineered the CAR-T cells and demonstrated their specificity for the extracellular matrix protein fibulin-3, which is secreted by MM cells. In the next year, this project will test the efficacy of the CAR-T cells to impair mesothelioma tumor growth using *in vivo* mouse models. This project represents a novel approach for CAR-T immunotherapy of solid tumors directed against a secreted target in the tumor microenvironment. 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 remains a respiratory risk in combat and disaster zones in countries that have not banned asbestos use.	*Presentation: 1*
CA160396 $612,000 Open	Gumperz/ University of Wisconsin at Madison	Modeling Human Gamma Delta T Cells as Antitumor Agents *In Vivo*	RP: This study will identify the signals 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 will observe their influence on tumor burden in these mice. MR: Previous findings highlight an association between exposure to military-relevant chemical mutagens (e.g., AO) or ionizing radiation, and an increased risk of B cell lymphoma development. Therefore, novel treatments of this disease would have a major impact on military personnel and their families.	*None to date*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
IMMUNOTHERAPY				
CA160461/P1/P2 $1,241,250 Open	Lee/ Research Institute at Nationwide Children's Hospital Cairo/ New York Medical College Seeger/ Children's Hospital, Los Angeles	Overcoming Immune Escape Mechanisms in Immunotherapy of Neuroblastoma	RP: The two major aims of this study are to (1) correlate persistence, phenotype, and anti-neuroblastoma function of activated natural killer (NK) cells to clinical outcomes of the NANT-2013 clinical trial; and (2) identify clinically translatable modifications to tumor microenvironment to improve clinical outcomes of the current neuroblastoma (NB) immunotherapy platform. MR: This proposal addresses childhood NB, the most common extracranial solid tumor among children and one that, by means of its poor survival rate, high morbidity, and protracted course, has a disproportionate effect on parents, including those in the military.	*None to date*
CA160480 $568,800 Open	Hsu/ University of Virginia	Diacylglycerol Activation of T-Cell Receptor Signaling for Cancer Immunotherapy	RP: This project is investigating a lipid kinase, diacylglycerol kinase alpha (DGKA), and its role in T cell activity and responsiveness in tumor microenvironments. The PI has discovered an inhibitor, RF001, which selectively targets and inhibits DGKA activity. In the next year, RF001 will be tested for its ability to modulate T cell biology and enhance anti-tumor immune responses. 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, shown to have a higher incidence in U.S. military population than in the general population, according to the DoD-published Automated Central Tumor Registry.	*Publications: 3* *Presentations: 6*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
IMMUNOTHERAPY				
CA160503 $644,894 Open	Wang/ University of Southern California	Engineering of Tumor-Selective CAR for Adoptive Cell Therapy Against Kidney Cancer	RP: The PI proposes developing and testing a new CAR that will be capable of reducing on-target, off-tumor adverse effects associated with kidney cancer immunotherapies. MR: Veterans who participated in radiation risk activities are at higher risk for cancers of the urinary tract, including renal cell carcinoma (RCC).	*New research – no outcomes reported to date*
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 monitor metabolism directly at 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 cultured in low glucose conditions *ex vivo* or while present in nutrient-poor environments, such as the tumor microenvironment. In the first year, the PI successfully developed methods that enable tracking of T cell function at the single-cell level. These studies will ultimately improve the efficacy of immunotherapies to treat leukemia and solid tumors. MR: The most recent and comprehensive study comparing the military population with the National Cancer Institute (NCI) Surveillance, Epidemiology, and End Results Program (SEER) demonstrated that the overall melanoma incidence rate among Active Duty military personnel was 62 percent greater than the general SEER population between 2000 and 2007.	*Publications: 4* *Presentations: 5*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
IMMUNOTHERAPY				
CA160714/P1/P2 $1,052,800 Open	Conforti; Wise-Draper/ University of Cincinnati Janssen/ Children's Hospital, Cincinnati	Ionic Mechanisms of Resistance to Immunotherapy in Head and Neck Cancer	RP: The objective of this study is to understand why immunotherapy works in some people and not for others. Focusing on the response or resistance to anti-PD1 therapy in head and neck squamous cell carcinoma (HNSCC) patients, the team is investigating whether proteins that regulate calcium and potassium signaling within immune cells could account for these differences in drug response. In the first year, the study team acquired data suggesting that anti-PD1 therapy has a positive effect on calcium signaling, which indicates T cell activation. Additionally, preliminary data show that the signaling molecule CD244 plays an inhibitory role in the antitumor immune response. Future work includes further examining these mechanisms in humanized mice. These studies will identify novel pathways involved in the anti-PD1 therapeutic response. MR: Each year, there are 400,000 new HNSCC case diagnoses, with an overall five-year survival rate of less than 50 percent for high-risk cases. Veterans have twice the prevalence of HNSCC compared to non-veterans.	*None to date*
CA160938 $231,656 Open	Shakiba/ Memorial Sloan Kettering Cancer Center	The Impact of TCR Affinity on T-Cell Dysfunction and Immunotherapeutic Reprogramming in Solid Tumors	RP: This project seeks to determine whether 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. Results from the first year show that high affinity interactions between T cells and tumors lead to a complete loss of function in the tumor-infiltrating T cells. Low affinity interactions maintain the function of T cells. This finding provides new insights into which T cells are best-suited for targeting tumors and could impact the development of immunotherapeutics. The second year of this project will focus on elucidating the molecular signaling pathways and gene expression patterns that allow the low-affinity T cells to maintain function. MR: This work will provide important insights into regulatory mechanisms of T-cell dysfunction in tumors, potentially leading to strategies for novel cancer immunotherapies.	*None to date*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
IMMUNOTHERAPY				
CA161007 $236,627 Open	Pituch/ Northwestern University	Combination of IL13Ralpha2 CAR T-Cell Therapy with PD-1 Immune Checkpoint Blockade for Treatment of Glioblastoma	RP: This study aims to determine the central mechanisms (1) regulating CAR T-cell homeostasis at the glioblastoma multiform (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 diagnosed people are between 45 and 70 years of age, and the majority of those diagnosed with GBM are men. These demographics also strongly coincide with our veteran population.	*Publication: 1* *Presentation: 1*
CA170734 $634,000 Open	Lim/ University of California, San Francisco	Engineering Next-Generation CAR T Cells to Treat Pediatric AML: Enhancing Safety Through Dynamic Control and Specificity	RP: This study intends to develop next-generation immunotherapy with enhanced specificity and reduced toxicity to treat acute myeloid leukemia (AML). MR: Military personnel and their children are at risk of developing clonal myeloid disorders due to potential exposures to radiation or chemical mutagens.	*New research – no outcomes reported to date*
CA171008 $640,000 Open	Reshef/ Columbia University Medical Center	Identification of Effector and Suppressive T-Cell Clones in Graft-vs-Host Disease	RP: This study aims to identify alloreactive T-cell clones in GvHD affected tissues and determine their individual function. MR: Blood cancers are more prevalent among young adults and children of Service members. Allogeneic stem cell transplant (SCT) is standard therapy for blood cancers, performed in approximately 30,000 people worldwide each year, including many military personnel.	*New research – no outcomes reported to date*
CA171068 $642,500 Open	Sarantopoulos/ Duke University	Breaking B-Cell Tolerance to Produce Antibodies that Eradicate Leukemias and Lymphomas	RP: This study intends to develop B-cell immunotherapies for the treatment of hematolymphoid malignancies. MR: Blood cancers, including lymphoma and multiple myeloma, are associated with exposure to chemical and biological agents from the Vietnam and Gulf Wars.	*New research – no outcomes reported to date*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
IMMUNOTHERAPY				
CA171157 $543,766 Open	DeKosky/ University of Kansas Center for Research, Inc.	High-Throughput TCR Repertoire-Based Platforms for Antigen-Specific Cancer Immunotherapy	RP: This study aims to develop new systems for rapid, personalized, and antigen-specific T-cell receptor (TCR)-based immunotherapy that involve the isolation and re-delivery of tumor-specific TCRs to cancer patients. MR: Military populations show enhanced risk of several cancer types due to service-related exposures. Immunotherapy has an outsized benefit for the care and treatment of military Service members through the immune system's targeting of neoantigens generated by such exposures.	*New research – no outcomes reported to date*
CA180380 $704,000 Under Neg	Pollack/ Fred Hutchinson Cancer Research Center	T-Cell Trafficking into the Cold Tumor Immune Microenvironment	RP: The goal of this project is to understand why the tumor microenvironment of soft tissue sarcomas (STS) do not support a sustained response to immunotherapy. The investigator plans to develop an *in vitro* organoid model that uses patient tumor samples and immune cells to improve the tumor microenvironment to support T cell function. MR: The prevalence of admission for sarcoma in the MHS has been estimated at 1.7 cases per 100,000 per year. Some soft tissue sarcomas are believed to be related to veterans' exposure to AO or other herbicides during military service.	*Research not yet initiated*
CA180681 $616,508 Under Neg	Byersdorfer/ University of Pittsburgh	Leveraging T-Cell Metabolism to Improve Anticancer Immunotherapies	RP: This project aims to improve anti-cancer immune responses, particularly in myeloma and leukemias. In 30 percent of patients, engineered immune cells do not live long enough in the body to effectively clear the cancer cells. The PI plans to modulate immune cells to enhance metabolic activity, which is hypothesized to improve tumor clearance. MR: Improved treatments for difficult-to-treat cancers is relevant to Active Duty Service members, veterans, their beneficiaries, and the American public, not only because of the sheer number of leukemia and myeloma cases diagnosed each year, but also because of the personal impact brought by each diagnosis.	*Research not yet initiated*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
IMMUNOTHERAPY				
CA180683/P1 $1,636,581 Under Neg	Fry/ University of Colorado at Denver Tasian/ Children's Hospital, Philadelphia	Precision Combinatorial Immunotherapeutic Targeting of Cytokine Receptor Kinase Signaling in CRLF2-Rearranged ALL	RP: This project aims to improve immunotherapies that target common mutations among pediatric and Down Syndrome leukemia patients. The investigators will develop new CAR-T cells that recognize these specific mutations to reduce the need for toxic chemotherapy and risk of relapse. MR: The development of novel immunotherapeutics have broad relevance in acute leukemias across the age spectrum, and are thus directly relevant to Active Duty military personnel, veterans, and their dependents who may develop leukemias.	*Research not yet initiated*
CA180733 $1,360,616 Under Neg	Snook/ Thomas Jefferson University	Clinical Translation of GUCY2C CAR-T-Cell Therapy	RP: The objective of this project is to translate the development of a new immunotherapy for GI cancers from the discovery phase into a product ready for clinical testing. The investigator will engineer patient immune cells to specifically target GI cancer cells. If pre-clinical *in vivo* studies are successful, the results will inform the initiation of a Phase I clinical trial. MR: In 2017, GI related malignancies were responsible for 20 percent of cancer-related deaths in the United States. New treatment strategies for GI cancers will reduce mortality and costs associated with disease management for the MHS.	*Research not yet initiated*
CA180898 $648,000 Under Neg	Reshef/ Columbia University Medical Center	Glucagonlike Peptide 2 (GLP-2) Analogues as a Novel Strategy for Prevention and Treatment of Graft-Versus-Host Disease	RP: Gut mucosal damage and graft-versus-host disease are common complications following bone marrow transplants. This project will use a drug that enhances intestinal growth and repair to improve outcomes among patients who receive a bone marrow transplant. MR: Blood cancers, such as lymphoma and leukemia, represent some of the more common cancer types. Their high prevalence in young adults and children makes it highly relevant for Service members and their families. Allogeneic SCT is standard therapy for blood cancers, performed in approximately 30,000 people worldwide each year, including many military personnel.	*Research not yet initiated*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
IMMUNOTHERAPY				
CA181002 $633,864 Under Neg	Chan/ Baylor College of Medicine	Tipping the DAMP/iDAMP Balance: Converting Immune Checkpoint Nonresponders into Responders	RP: Over 70 percent of patients do not respond to immunotherapy treatments. This project will investigate mechanisms to improve immunotherapy outcomes. The investigator aims to identify FDA-approved drugs that can convert immune cells to specifically kill cancer cells. MR: Elderly veterans are impacted by bladder, pancreatic, and colon cancer diagnoses, which generally do not respond to immunotherapy.	*Research not yet initiated*
CA181035 $565,375 Under Neg	Han/ University of Massachusetts Medical School	Photoregulated Immunotherapy	RP: The goal of this project is to reduce side effects following CAR-T cell immunotherapy. T cells will be engineered to contain an "on/off switch" that responds to optical stimulation *in vivo*. MR: B cell lymphoma is known to be related to veterans, surviving spouses, dependent children, and dependent parents of veterans exposed to herbicides during military service.	*Research not yet initiated*
CA181486 $576,000 Under Neg	Mazur/ The University of Texas MD Anderson Cancer Center	Transcription Control of Exhaustion Program in CAR T-Cell Therapy	RP: This project aims to enhance the efficacy of CAR T-cell therapy for the treatment of pancreatic cancer. This study will employ computational biology screens to identify genetic factors that will improve CAR T-cell mediated killing of cancer cells. Results of the screen will be validated with pre-clinical mouse models of pancreatic cancer. MR: Military personnel are at higher risk of developing pancreatic ductal adenocarcinoma (PDAC) due to occupational exposures to cancer risk factors. Improving treatments for PDAC will have an impact on Service members and veterans.	*Research not yet initiated*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
KIDNEY CANCER				
CA150395 $569,236 Open	Leppert/ Stanford University	IQGAP1 Scaffold-Kinase Interaction Blockade in Renal Cell Carcinoma: A Novel Biomarker and Therapeutic Strategy	RP: The intracellular scaffold protein IQGAP1 is required for ERK1/2-driven tumor progression. In this study, the PI is evaluating IQGAP1 expression in renal cell carcinoma (RCC) tumors, and correlating this to RAS signaling (the signaling pathway that involves ERK1/2) and clinical outcomes. Additionally, the PI is studying IQGAP1 inhibitors in tissue slice cultures and patient-derived xenograft models. MR: Veterans and military beneficiaries represent a highly relevant population at risk of developing RCC, due to the predominantly male population diagnosed with 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 from the Veterans Health Administration.	*Publication: 1*
CA160279 $597,600 Open	Ho/ Mayo Clinic and Foundation, Scottsdale	Reprogramming Chromatin Modifiers in Kidney Cancer	RP: This study aims to improve 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 life lost. Therefore, improved ability to detect those most likely to experience RCC recurrence would be beneficial to members of the military and their beneficiaries.	*Publication: 1* *Funding Obtained: 1*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
KIDNEY CANCER				
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.	*None to date*
CA160728/P1/P2 $686,909 Open	Jonasch/ The University of Texas MD Anderson Cancer Center Rathmell; Haake/ Vanderbilt University Medical Center	Prognostic and Predictive Markers of Immunogenicity in Renal Cell Carcinoma	RP: In this study, the PIs will use RCC samples collected from multiple trials, including one VA trial, to assess: (1) whether certain chromatin remodeling mutations ultimately influence T cell tumor infiltration, and to determine if the tumor's genomic background 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 affect 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 of which are factors prevalent among military members. The predictive biomarkers developed under this grant will fundamentally alter the approach taken to treat military patients with advanced RCC.	*None to date*

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: This project aims to create a novel CRC vaccine. The vaccine uses inactive Listeria bacteria to express a CRC protein, GUCY2C, which will ultimately induce a T cell response to target and kill CRC cells. Upon optimization of the vaccine design, the study will test the vaccine's efficacy *in vivo* using mouse models. If successful, the results of this project will produce alternative treatment strategies for metastatic CRC, which is often fatal and for which there are few effective therapeutics. MR: CRC is the fourth most common neoplasm, with approximately 150,000 new cases per year, and is the second leading cause of cancer mortality among civilian and military populations, with a mortality of about 50 percent. The military has a unique increased burden for this disease, due to its population being of relatively younger age (less than 50 years of age) than the general population. Additionally, these patients present with advanced disease, which is more likely to recur.	*None to date*
CA171143 $564,498 Open	Sheridan/ Stony Brook University	Using Oral Delivery of Listeria-Based Cancer Vaccines to Target Gastrointestinal Cancers	RP: This project seeks to test the utility of a new orally delivered listeria-based vaccine. The study will compare the efficacy of the oral vaccine to intravenous immunization in mice models of CRC. MR: Gastrointestinal cancers are the third most common cancers among VA patient populations.	*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				
CA150178 $610,200 Open	Lujambio/ Icahn School of Medicine at Mount Sinai	Functional Genomics Screen for Combination Therapy Discovery in Liver Cancer	RP: This study intends to develop new combinatorial therapies for hepatocellular carcinoma (HCC) that increase the efficacy of palbaciclib, an FDA-approved cancer treatment. Lead targets for combination therapy with palbaciclib were identified, and validation of their synergistic anti-tumor effect is underway. MR: HCC incidence is increasing in the United States, especially within the military and veteran communities. Most of the main risk factors for HCC, such as alcohol consumption, hepatitis B virus (HBV) infection, hepatitis C virus (HCV) infection, obesity, and male gender, are over-represented within the U.S. military and veteran populations.	*Presentation: 1*
CA150245/P1/ P2/P3/P4 $1,411,884 Open	Zhu; Yopp; Singal; Siegwart/ University of Texas Southwestern Medical Center at Dallas Waljee/ University of Michigan	Defining Hepatocellular Carcinoma Subtypes and Treatment Responses in Patient-Derived Tumorgrafts	RP: This study aims to enhance understanding of the basic biology of HCC at different disease stages. Patient-derived xenografts from over 100 HCC cases have been collected. During the second year of this award, the study will establish the molecular signature of these cancers, and investigate their susceptibility to small RNA therapies. 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 its higher rates of 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.	*Publication: 1* *Funding Obtained: 1*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
LIVER CANCER				
CA150248 $613,200 Open	Lau/ Northern California Institute for Research and Education	The Genetic Basis of Sex Differences in Liver Cancer	RP: This study aims to validate a male-specific cancer gene, TSPY, as a diagnostic and predictive marker in liver cancer. The PI is working to establish the contribution of TSPY and other Y chromosome-expressed genes to liver cancer pathology. Overexpression of TSPY seems to support a pro-proliferation phenotype in HCC cells, while another Y chromosome-expressed gene RBMY shows a bimodal effect. MR: Risk factors pertaining to liver cancer are most prevalent among military members and veterans. The proposed research plans to validate TSPY as a diagnostic and predictive marker of liver cancer, using patients from the San Francisco VA Medical Center.	*Publications: 2* *Presentations: 2*
CA150262 $437,152 Open	Albrecht/ VA Medical Center Minneapolis, MN	The Role of CDK2 in Hepatocellular Carcinoma	RP: This study seeks to explore the mechanisms by which cell cycle regulator CDK2 contributes to HCC. The PI has confirmed that loss of CDK2 expression is highly protective against HCC development, and in the next year of the award will identify genes contributing to cdk2-induced pathology. MR: The proposed research is highly relevant to military veterans due to the increasing incidence of HCC in this population.	*None to date*
CA150272/P1/ P2/P3/P4 $1,628,557 Open	Friedman; Llovet; Lujambo; Villanueva/ Icahn School of Medicine at Mount Sinai Lowe/ Memorial Sloan Kettering Cancer Center	Mechanisms of Acquired Resistance to Sorafenib in Hepatocellular Carcinoma	RP: This study aims to identify the critical elements of resistance to sorafenib and other HCC therapies. Using a combination of patient-derived biopsies, three-dimensional (3D) cultured organoids, and tumor stroma samples, this study will investigate the molecular mechanism of resistance, as well as identify and validate second-line drug targets. MR: HCC incidence is increasing in the United States, especially within the military and veteran communities. Among the main risk factors for HCC development are alcohol consumption, HBV infection, HCV infection, obesity, and male gender, all of which are over-represented in the U.S. military and veteran populations.	*None to date*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
LIVER CANCER				
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: This study seeks to develop an experimental system that will enable identification of cancer prevention targets and biomarkers of liver cancer post-HCV clearance. This study will use a cell-based model to describe molecular changes that occur at the transcriptome, epigenome, and secretomic levels resulting from oncogenic HCV infection. MR: Prevalence of HCV infection among U.S. veterans is more than threefold higher than in the U.S. general population. The number of veterans with HCV-related liver cancer has increased ninefold over the past decade.	*Presentation: 1* *Publications: 11*
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: This study aims to develop a novel way to enhance therapeutic efficacy of FDA-approved immune checkpoint inhibitors against liver cancer. It will examine whether inhibition of Angpt1, a potential target of established oncogenes, will contribute to enhanced tumor clearance in mouse models of hepatic cancer. In the first year of the award, the PI established that Angpt1 inhibition enhances the PD-1/PD-L1/2 inhibitor-mediated anti-HCC immunity and extends the mouse survival rates. MR: Rates of liver cancer are on the rise in Western countries, largely due to obesity and HCV infection, as there is no vaccine for HCV. Military personnel have an increased chance of viral infection during deployment and combat, and are at higher risk of developing liver cancer.	*None 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 $1,323,046 Open	Schook/ University of Illinois at Urbana-Champaign Solomon; Brown; Boas/ Memorial Sloan Kettering Cancer Center Gaba/ University of Illinois at Chicago	Genetically Inducible Porcine Model of Primary and Metastatic HCC in Comorbidity Host Environments for Interventional Radiology-Guided Detection and Treatment	RP: This study aims to develop a porcine model of HCC. The study entails characterization of porcine HCC in comparison to the human disease to determine the utility of the model system for disease progression, tumor host environmental effects, and disease treatment strategies. As of Year One, transgenic pigs are generated and ready for characterization. Tumors have been developed and resected in multiple pigs; characterization and staging of tumors is ongoing. Tumors are also being monitored through imaging protocols. MR: HCC is exceedingly common in the U.S. veteran population due to a high incidence of alcoholic cirrhosis and viral hepatitis.	*Presentations: 9* *Publication: 3* *Miscellaneous: 1* ***Start-up company based off of this technology was initiated*
CA150850 $108,969 Open	Liu/ Massachusetts General Hospital	Molecular Characterization of FGFR2 Fusions in Cholangiocarcinoma	RP: This study seeks 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). The study entails engineering a new mouse model of ICC and testing of small molecule inhibitors of FGFR signaling 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 one year of diagnosis, and treatment with chemotherapy has limited effectiveness. ICC risk factors are similar to those of other chronic liver diseases, including chronic alcohol consumption, obesity, and viral hepatitis - all of which affect military personnel and veterans.	*None to date*

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 Percent of Human Liver Cancer, and Major Determinant of Response to Sorafenib	RP: This project aims to describe the mechanism by which LSP1 negatively interferes with the effectiveness of Sorafenib. Findings from this research would support the use of LSP1 expression in tumors as a novel predictive biomarker of patient response to Sorafenib. A second arm of this project aims to investigate whether drugs that block modification of LSP1 could reinforce the tumor-suppressive effect of unmodified LSP1 in HCC. MR: U.S. military personnel have unique exposure-related risks associated with development of HCC. AO, pesticides, industrial solvents, and polychlorinated biphenyl (PCB) are all military relevant agents associated with increased risk of HCC.	*Publication: 1*
CA160216/P1/P2 $905,558 Open	Bardeesy; Zhu/ Massachusetts General Hospital Shokat/ University of California at San Francisco	A Proteomic Co-Clinical Trial of BGJ-398 in FGFR-Driven Biliary Cancers	RP: The goal of this study is to understand the biological consequences of fibroblast growth factor receptor (FGFR) alterations that drive biliary tract cancers. The research team aims to identify how FGFR mutations alter signaling and how these cells respond to FGFR inhibition. Additionally, the team will identify genetic mechanisms that contribute to the acquired resistance to FGFR inhibition, and will develop therapeutic strategies to prevent or overcome resistance. Currently, the research team has created multiple cell lines with different FGFR mutations, and identified additional cell lines that are resistant to FGFR inhibitors. MR: More than 1 in 20 cancer patients have a tumor with an FGFR mutation. This includes many cancers with higher incidence in the veteran population, including biliary tract tumors, for which liver cancer is only one example. The increased rates of HCV infection and liver fluke exposure within this population make biliary tract tumors an important veterans' health issue.	*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				
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, the study team will perform all necessary preclinical testing to evaluate safety and drug delivery efficacy. MR: The VA recognizes liver cancer (HCC) as a risk factor related to HCV infection or ionizing radiation exposure during military service.	*Presentations: 2* *Publications: 3*
CA160466 $598,070 Open	Simon/ Rockefeller University	Therapy for the Adolescent/Young Adult Cancer Fibrolamellar Hepatocellular Carcinoma	RP: Study findings regarding fibrolamellar carcinoma (FLC), a lethal liver cancer, highlight the presence of a genetic deletion that results in the fusion of a heat shock protein (DNAJB1) and a protein kinase (PRKACA) in 100 percent of FLC patients. Presence of this fusion protein is sufficient to induce FLC in mouse models. The objective of this study is to identify molecules that block the function of this protein or target it for degradation. MR: Fibrolamellar diagnosis can occur among adolescents and young adults, underscoring that Active Duty military, as well as their children, are in the affected age group.	*Publications: 2*
CA160545 $644,754 Open	Welling III/ University of Michigan, Ann Arbor	Therapeutic Targeting of Cancer Stem Cells in Liver Cancer	RP: This project will focus on the preclinical assessment of two novel HCC therapies. Using cholangiocarcinoma, HCC patient-derived xenografts, and a mouse model of HCC, the PI will assess the impact of these drugs on liver cancer development *in vivo*. MR: Cholangiocarcinoma (CCA), the second most common primary liver cancer, arises most frequently during the presence of chronic liver disease, which affects 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 three months.	*None to date*

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 inquires 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 will observe the incidence of liver cancer *in vivo*. MR: Broadening our understanding of the genetic, cellular, and molecular basis of liver cancer development could lead to the identification of biomarkers for the early detection of liver cancer. This has great potential to impact Service members and their families, given that the military population is particularly vulnerable to this cancer.	*None to date*
CA170048 $563,949 Open	Sarkar/ Virginia Commonwealth University	TAF2: A Potential Oncogene for Hepatocellular Carcinoma (HCC)	RP: This study aims to examine the role of TAF2 as an oncogene in HCC and determine whether it is a potential target for therapeutics. The research team will accomplish this by overexpressing and deleting TAF2 in cultured HCC cells and in mice. The research team will then use patient-derived HCC tumor samples to establish HCC in mice, and use siRNA to block TAF2 *in vivo*. MR: Incidence of HCC in the veteran population has been increasing from 2001 to 2013 due to non-alcoholic fatty liver disease and alcoholic cirrhosis.	*New research – no outcomes reported to date*
CA170103 $669,999 Open	Wajapeyee/ Yale University	A Druggable Epigenetic Vulnerability Pathway in p53-Deficient Hepatocellular Carcinoma	RP: This study intends to explore the therapeutic potential of DOT1L, an epigenetic regulator, as a target for treating certain populations of HCC. The project will investigate the role of DOT1L in maintaining HCC tumor growth and metastasis *in vivo*, and will evaluate the utility of pharmacological targeting of DOT1L. MR: HCC is significantly higher among military personnel than the general population due to exposure to liver carcinogens while on duty locations.	*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				
CA170172 $639,600 Open	Nieto/ University of Illinois at Chicago	Role of Osteopontin in Hepatocellular Carcinoma	RP: This project will examine the biological contribution of osteopontin (OPN) to hepatocellular carcinogenesis. The PI will utilize well-established mouse models of HCC to investigate the impact of OPN *in vivo*. MR: HCC remains difficult to treat, and the only approved oral treatment (Sorafenib) prolongs the median lifespan by about two months. This project could identify new potential targets for future treatment.	*New research – no outcomes reported to date*
CA170574 $533,188 Open	Ploss/ Princeton University	Modeling Human Hepatocellular Carcinoma in Humanized Mice	RP: This study aims to understand the role that various mutations play in the formation and growth of HCC, with the hope of identifying targeted therapeutics for HCC. The investigator plans to engraft human liver cells in mice, then use CRISPR technology to disrupt genes commonly associated with the development of HCC to study the molecular processes involved in HCC development. MR: Incidence of liver cancer has been increasing from 2001 to 2013 in the veteran population.	*New research – no outcomes reported to date*
CA170674 $1,114,344 Open	Marks/ Naval Medical Center, San Diego Sirlin/ University of California, San Diego Loomba/ University of California, San Diego	Abbreviated Magnetic Resonance Imaging and Biomarker-Based Detection of Early Liver Cancer	RP: This prospective study aims to compare a newly developed scanning method for HCC detection. The research team will compare the diagnostic accuracy of conventional ultrasound screening with its new abbreviated MRI (AMRI) method across 200 patients, military and civilian, with chronic liver disease. MR: Growing evidence indicates that both HCC and its major risk factors, including alcoholism, HCV, and chronic HBV infection, disproportionally affect the U.S. military population, beneficiaries, 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
LIVER CANCER				
CA170694 $558,000 Open	Burgoyne/ University of California, San Diego	Development of a Cellular State Prediction Model of Sensitivity and Resistance to Dual PI3K/BET Inhibitors in Hepatocellular Carcinoma	RP: This project intends to refine a new classification system for HCC tumors to predict drug sensitivity. The PI will utilize drug responsive and resistant tumor cells from HCC patients to improve the accuracy of this predictive model, and identify cellular targets that may contribute to drug resistance. MR: The prevalence of HCV is at least twofold higher in the veteran population than in the general U.S. population. Additionally, two-thirds of veterans with HCC have an HCV infection.	*New research – no outcomes reported to date*
CA171017 $572,400 Open	Smoot/ Mayo Clinic and Foundation, Rochester	Mechanisms of Oncogenesis in the Primary Liver Cell Cancer Cholangiocarcinoma	RP: This study will identify whether members of the Src family of kinases are able to regulate signaling pathways, which are associated with cholangiocarcinoma, a specific type of liver cancer. MR: The U.S. veteran population has a higher prevalence of HCV infection than the general U.S. population. This infection doubles the risk of developing cholangiocarcinoma.	*New research – no outcomes reported to date*
CA180064/P2 $1,710,189 Under Neg	Javle/ The University of Texas MD Anderson Cancer Center Azad/ Johns Hopkins University	Genomic/Immunological Heterogeneity of Intrahepatic Cholangiocarcinoma: Clinical and Translational Studies by International Cholangiocarcinoma Research Network	RP: This study will use gene expression profiling to characterize the genetic and immunologic heterogeneity of intraheptic cholangiocarcinoma (IHCCA); identify biomarkers and mechanisms of drug resistance; and explore novel checkpoint inhibitor combinations in preclinical models. MR: Veterans, Active Duty military personnel, and their beneficiaries are at risk of developing IHCCA, the second most common primary liver cancer. Results from this study could provide information on how IHCCA patients will respond to treatments, and identify novel combination therapies.	*Research not yet initiated*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
LIVER CANCER				
CA180097 $1,667,982 Under Neg	Duda/ Massachusetts General Hospital	Role and Biomarker Value for Plasma HGF in Susceptibility to High-Dose Radiation-Induced Liver Dysfunction	RP: This study will assess the efficacy and safety of hypofractionated radiotherapy in treating HCC, as well as validate the use of hepatocyte growth factor (HGF) as a biomarker for susceptibility to radiation-induced liver damage in HCC patients. MR: Active Duty military, veterans, and their beneficiaries are at risk for developing HCC, which has been increasing in prevalence. Risk factors include poor nutrition, repeated exposure to toxins, and being of the male gender. This greatly affects mission readiness, given that military personnel are exposed to these high-risk factors. This study could identity a biomarker to predict susceptibility to radiation-induced liver damage during treatment, which could lead to preventative approaches to mitigate this type of liver damage during treatment.	*Research not yet initiated*
CA180296 $579,103 Under Neg	Xie/ East Tennessee State University	Met-Targeting Chimeric Antigen Receptor (MetCAR) T-Cell Therapy in Hepatocellular Carcinoma	RP: This study will investigate the therapeutic potential of Met-targeting CAR T cells in advanced HCC. MR: Military members and their beneficiaries are at increased risk of developing HCC due to exposure to toxins and higher rates of HBV/HCV infections that lead to hepatitis. This study could offer a new T-cell based therapy to treat HCC.	*Research not yet initiated*
CA180361 $607,000 Under Neg	Zhang/ Tulane University	The Long Noncoding RNA CRNDE in HCC-Induced Immune Suppression	RP: The goals of this study are to establish an effective approach to treat HCC through counteracting CRNDE with next generation anti-sense oligonucleotides, and to evaluate whether CRNDE may be used in concert with existing therapeutics to treat HCC. MR: HCC is more prevalent among men, who comprise 85 percent of the military population. Thus, HCC poses a threat to mission readiness. This study may yield a new therapeutic strategy for treatment of HCC.	*Research not yet initiated*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
LIVER CANCER				
CA180366 $669,999 Under Neg	Wajapeyee/ Yale University	A Novel Therapeutic Approach for Treating WNT-Driven Hepatocellular Carcinoma	RP: This study will investigate the role of SETD7 in the growth of WNT-driven HCC tumors. The PI will use small-molecule drugs to target SETD7 in preclinical mouse models to study HCC growth and progression, and evaluate therapeutic potential. MR: HCC has a higher prevalence among military personnel than the general population, partially due to exposure to liver carcinogens. This study could lead to new treatment options targeting SETD7 in liver tumors.	*Research not yet initiated*
CA180436 $624,000 Under Neg	Finn/ University of California, Los Angeles	Development of Novel Antibody-Drug Conjugates (ADCs) for the Treatment of Advanced Liver Cancer	RP: The objectives of this study are to generate a panel of monoclonal antibodies targeted specifically to HCC; determine which monoclonal antibodies are candidates for drug development; and perform safety/toxicity studies with the candidate drug. MR: There is high incidence of HCC among military personnel, especially the veteran population. The proposed studies could validate new drug targets for HCC treatment, which would improve outcomes for patients.	*Research not yet initiated*
CA180499 $538,270 Under Neg	Shi/ Brigham and Women's Hospital	Combination of p53 mRNA Nanotherapy with Immunotherapy for Liver Cancer Treatment	RP: This project will seek to develop a novel and effective therapeutic strategy for HCC treatment, by generating an effective and safe messenger RNA (mRNA) nanotherapy candidate that could benefit HCC patients with p53 loss/mutation. It will also examine mechanisms of anti-tumor immune responses. MR: There is a high incidence of HCC among military veterans. This proposed research could lead to the development of a new specialized treatment for HCC, which would improve prognosis of this disease.	*Research not yet initiated*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
LIVER CANCER				
CA181246 $559,800 Under Neg	Raab/ University of North Carolina at Chapel Hill	Mechanistic Analysis of ARID Mutations in Hepatocellular Carcinoma	RP: Mutations in chromatin remodelers, especially genes involved in the SWItch/Sucrose Non-Fermentable (SWI/SNF) complex, are frequent in liver cancer. The PI hypothesizes that altered SWI/SNF composition and targeting underlies chromatin changes in liver cancer. This study will characterize changes to SWI/SNF composition; identify the role of SWI/SNF on altering the chromatin environment in the liver; and generate novel SWI/SNF-dependent liver tumor models. MR: Liver cancer incidence is rising in the United States and affects Active Duty military personnel, veterans, and their beneficiaries. Mutations in SWI/SNF subunits are common in liver cancer; however, there are currently no therapeutic targets due to a lack of understanding the role of this complex. This study will provide new knowledge on the role the SWI/SNF complex plays in liver cancer development and progression, which could lead to new drug targets.	*Research not yet initiated*
CA181430 $581,400 Under Neg	Wilkins/ University of Virginia	Development of Novel Embolization Therapy for Hepatocellular Carcinoma	RP: The goal of this study is to test whether natural phytochemical caffeic acid can enhance drug delivery to HCC cells and improve treatment efficacy. MR: HCC is growing in incidence and has high prevalence among Active Duty Service members and veterans. This project could lead to advances in drug delivery to tumors, which would improve HCC outcomes.	*Research not yet initiated*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
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 the 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, as well as the sensitivity of ABC-DLBCL to MALT1 inhibitors. MR: Military personnel are at greater risk of developing Non-Hodgkin's lymphoma (NHL) from exposure to cytotoxins and chemicals. DLBCL is one of the most aggressive and chemoresistant forms of NHL.	*Publication: 1* *Presentations: 4*
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.	*Presentations: 2*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
LYMPHOMA				
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: The aim of this project is 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 are at 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 that target lymphoma.	*Publication: 1* *Presentation: 1*
CA170783 $692,000 Open	Kwak/ City of Hope Beckman Research Institute	Novel CAR-T Therapy Targeting BAFF-R Against B-Cell Lymphomas	RP: The purpose of this study is to develop a new CAR-T cell therapy for patients with B-cell NHL. MR: Military personnel are at greater risk of lymphoma due to deployment-related exposures. CAR-T therapy has the potential to cure lymphomas.	*None to date*
CA170924/P1/P3 $1,159,665 Open	Ansell/ Mayo Clinic and Foundation, Rochester Lazaryan/ University of Minnesota Twin Cities Villasboas; Bisneto/ Mayo Clinic and Foundation, Rochester	Promoting an Effective Antitumor Immune Response in Lymphoma	RP: The aim of this study is to use the activation of suppressed effector cells and immune exhausted T-cells to induce an effective antitumor response in B-cell NHL. MR: Military personnel are at greater risk for developing NHL from exposures to cytotoxins and chemicals during deployment. This study will enhance the intrinsic immune function to mount an effective antitumor immune response.	*Presentations: 2*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
LYMPHOMA				
CA171169 $575,997 Open	Leeman-Neill/ Columbia University Medical Center	The Role of Activation-Induced Cytidine Deaminase in Pesticide-Related Lymphomagenesis	RP: The purpose of this study is to evaluate the effects of pesticides on activation-induced cytidine deaminase (AID) mediated mutagenesis and lymphomagenesis, and to elucidate the mechanism that links pesticide exposure to increased AID-expression and aberrant somatic hypermutation. MR: Military personnel experience a significant degree of pesticide exposure, and have been found to experience adverse health effects due to these exposures.	*None to date*
CA180262 $542,915 Open	Eischen/ Thomas Jefferson University	Targeting Mdm2 in Lymphoma	RP: The purpose of this study is to test the hypothesis that inhibition of Mdm2 will activate p53, which could induce cancer cell deaths in human DLBCL. MR: Exposure to chemicals and ionizing radiation are linked to lymphoma development. This study could potentially lead to advancement in DLBCL and new therapy for lymphoma.	*Research not yet initiated*
MELANOMA/SKIN CANCER				
CA150055 $631,883 Open	Kadekaro/ University of Cincinnati	Exploring a New Paradigm in Melanoma Prevention	RP: This study aims to determine whether a correlation exists between reactive oxygen species and induction of mutagenic DNA lesions within sun-exposed skin. The PI is currently investigating a newly developed class of antioxidants for their ability to prevent ultraviolet (UV)-induced DNA damage. The investigator has shown that *in vitro* cultures of human skin samples are excellent models to assess DNA damage and the impact of topical application of antioxidants. In the next year, animal studies will be performed to confirm the *in vitro* studies. 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 comprise 71 percent of the total enlisted military personnel. The expanded knowledge of melanoma initiation gained from this study could lead to improved interventions that protect our Service members and the general public from developing melanoma.	*Publication: 1*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
MELANOMA/SKIN CANCER				
CA150068 $558,000 Open	Moon/ University of Michigan	A New Vaccination Strategy for Treatment of Melanoma	RP: This study intends to develop new technology to induce potent immune responses against primary and metastatic melanoma using melanoma cell lysate-loaded nanoparticles. The investigator has developed a new method called NanoFACS that aids in characterizing the nanoparticles. Using an *in vivo* model of melanoma, the nanoparticle vaccines significantly reduce melanoma growth and promote T-cell activation. The final year of this project will test the nanoparticle vaccines with current immunotherapy drugs to treat melanoma *in vivo*. MR: Melanoma is of particular interest to the U.S. military due to the frequent exposure of military personnel 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.	*Publications: 10* *Presentations: 19*
CA150256 $617,020 Open	White/ Cornell University Ithaca	Defining the Role of Stem Cell Activation in Initiating Melanoma and Melanocytic Tumor Recurrence	RP: The goals of this research are to define the role of melanocyte stem cells (MCSC) in melanoma growth, and determine whether "slow-cycling cells" within the tumor are resistant to chemotherapeutics. The PI has demonstrated that MCSC activation facilitates rapid onset of tumor growth. MCSCs protected from ultraviolet B (UVB) remained in quiescence and did not initiate tumors. To study the slow-cycling cells, a novel mouse model was developed to allow for cell tracking during and after drug treatment. Results show that the slow-cycling cells are resistant to drug treatment. These results suggest that cancer drug development should examine the capability of the candidate drug to kill all cells within the tumor, not just the rapidly growing cells. MR: Military members recently deployed to Iraq and Afghanistan report excessive levels of sunlight exposure, causing concern for their heightened risk for melanoma.	*Publications: 2* *Presentations: 5*

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: This project aims to investigate the utility of the polyamine transport system (PTS) as a therapeutic target for drug-resistant melanoma tumor cells. Melanoma cell lines with induced BRAF inhibitor resistance have higher polyamine transport activity. A novel drug developed by the research team is able to enter cells with increased PTS activity to kill the tumor cells. This project adds to the understanding of the PTC in cancer cells, and how to utilize this transport system to treat resistant forms of melanoma. 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 that of the general population. Thus, military personnel across multiple branches of the military will also clearly benefit from new medical intervention.	*Presentations: 4* *Publications: 2* *Patent: 1*
CA150437 $610,200 Open	Moubarak/ New York University School of Medicine	Functional Role of Epigenetic Regulation in Melanoma Brain Metastasis	RP: The purpose of this study is to investigate the role of epigenetic regulators PHF8 and CHD7 in metastatic melanoma. PHF8 and CHD7 are upregulated in metastatic melanoma and required for melanoma invasion. The investigator has found that PHF8 controls transcription of genes in the TGF-beta pathway. Treatment of cells with a TGF-beta inhibitor suppresses PHF-8 mediated cellular invasion. This suggests TGF-beta inhibitors should be considered as a therapeutic option to prevent metastatic melanoma. The investigator will continue to explore transcriptional regulation by PHF8 and CHD7, and whether these two proteins can predict prognosis and treatment outcomes in metastatic melanoma patients. MR: Military personnel are exposed to UV-induced melanoma burden. Since 50 percent of metastatic melanomas ultimately lead to brain metastasis, gaining an understanding of the mechanisms of metastasis and conception of novel therapies are crucial for advances in patient care for Service members, their families, and other military beneficiaries.	*Publications: 2*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
MELANOMA/SKIN CANCER				
CA150523 $528,801 Open	Thomas/ Georgia Tech Research Corporation	Targeted Immunotherapy for Melanoma	RP: This project is evaluating whether the immunotherapy treatment process can be improved by conjugating a nanoparticle to the therapeutic antibodies to localize delivery to the lymph nodes or directly into the tumor. The PI has successfully developed drug-conjugated nanoparticles. Initial *in vivo* studies show that this method of localized immunotherapy significantly inhibits melanoma tumor growth, and improves survival and anti-tumor immunity in mouse models. In the last year of the award, the PI will investigate using multiple targeted therapeutic antibodies for melanoma treatment, and analyze the immune response to the nanoparticle conjugated antibodies. MR: Melanoma disproportionately affects U.S. military personnel, suggesting a role for military service-related exposure to carcinogens.	*Publications: 2*
CA150619/P1/P2 $720,000 Open	Herlyn/ Wistar Institute Cooper; Wargo/ University of Texas MD Anderson Cancer Center	Understanding the Immune Biology of Checkpoint Inhibitors to Develop New Strategies for Therapy	RP: The purpose of this study is to 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. Melanoma samples have been collected from 30 patients before and after treatment with the immunotherapies. To study the immune response to human melanoma and how immunotherapies affect immune cell infiltration into the tumors, two mouse models have been established where human immune cells have been reconstituted in the mice. Improved understanding of the mechanisms of action for checkpoint inhibitors *in vivo* will result in better design of combination drug studies for advanced melanoma. MR: Eighty-five percent of all melanomas are induced by excessive sun exposure, which many Service members had to confront during the last 15 years. Starting in the near future, the incidence of melanoma (and other skin cancers) is expected to drastically increase in Active Duty members and veterans.	*Publication: 1* *Presentation: 1*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
MELANOMA/SKIN CANCER				
CA150630/P1/P2 $1,520,000 Open	Weber/ New York University School of Medicine Gabrilovich; Hu/ Wistar Institute	Myeloid-Derived Suppressor Cells in Checkpoint Protein Inhibition for Melanoma	RP: This project is evaluating the immunoregulatory activity of a therapeutic antibody (DS-8273a), and its ability to trigger apoptosis of myeloid-derived suppressor cells (MDSCs). DS-8273a is administered in combination with the immunotherapeutic nivolumab in patients with unresectable Stage III or Stage IV melanoma. The investigators are currently completing the dose escalation studies of DS-8273a, and starting to analyze the specific mechanisms by which DS-8273a depletes MDSCs. Initial phenotyping of blood samples shows that responders express lower frequencies of MDSCs at baseline, and are further downregulated during treatment. Results from this project could lead to new methods of modulating the patient's immune system to treat melanoma and other cancers. MR: Active Duty Service members are at increased risk of melanoma due to high levels of sunlight exposure, the most significant risk factor for melanoma in most areas of the world in which the U.S. military is currently engaged.	*None to date*
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 (CTCs) 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 CTCs found in their blood. In the first year of this project, methods to isolate and enrich CTCs have been optimized, and patient accrual for the study has 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.	*None to date*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
MELANOMA/SKIN CANCER				
CA160224 $510,231 Open	Wallace/ Kansas State University	Cutaneous Human Papillomaviruses as Cofactors in Nonmelanoma Skin Cancer	RP: This project is investigating the mechanism by which transient human papillomavirus (HPV) infection drives increased risk for melanoma and other skin cancers. Using human skin cancer cell lines, the PI has shown that HPV proteins affect three cellular pathways that protect genome fidelity. In particular, HPV proteins block cells from repairing DNA damage resulting from UV and radiation exposure, and therefore increase the odds that harmful mutations will accumulate in skin cells. In the next year, the investigator will explore which cellular proteins interact with the viral proteins. MR: Extensive attempts to minimize the risk posed by UV 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 contribute to the high prevalence of these malignancies.	*Presentations: 5* *Publications: 2*
CA160347 $694,500 Open	Lian/ Brigham and Women's Hospital	Epigenetic Reprogramming and Skin Cancer Prevention	RP: This project will 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*. MR: Melanoma and SCC are of particular interest to DoD, due to occupational exposures to UV radiation and higher incidence of skin cancers among military personnel.	*Publication: 1*

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 is investigating how a clonal population of cells becomes the dominant components of solid tumors. Using a novel fluorescent assay to track cell lineage, the investigator is able to observe the process of clonal emergence in real time. Initial *in vitro* experiments suggest that antagonism between two oncogenes, such as BRAF and NRAS, are a potential mechanism for cellular competition, and have identified inhibition of the MAPK pathway as a mediator of this mechanism. The second year of the award will use *in vivo* models to corroborate these mechanisms. Results from this project will advance our understanding of why solid tumors are clonally heterogeneous. 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 $100M per year, not accounting for metastatic disease that develops from melanomas.	*Publication: 1* *Presentations: 4*
CA160489 $576,000 Open	Rai/ The University of Texas MD Anderson Cancer Center	Epigenetic Effectors of Tumor Response to Immune Checkpoint Inhibitors	RP: This project seeks to determine whether DNA modification states associate with immune checkpoint inhibitor response in melanoma. The PI is collecting tumor samples from patients treated with anti-PD1, and analyzing epigenetic markers to determine whether any correlations exist with clinical outcomes. Additionally, *in vivo* studies have shown that drugs that inhibit a class of DNA modifying proteins enhance anti-PD1 treatment in melanoma models. Results from this project will inform future clinical trials intending to target epigenetic proteins. MR: Military personnel are at an increased risk for developing melanoma, since Active Duty personnel are often required to be outside for prolonged periods and may be exposed to potential risk factors, such as UV rays from sunlight.	*Funding Obtained: 3*

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: In this study, the PI will investigate the role of B cells in enhancing the anti-melanoma activity of CD8+ T cells. Initial animal studies demonstrate that B cells play an important role in enhancing the therapeutic efficacy of immunotherapies to treat melanoma. This work could influence the field of immunotherapy drug development and identify biomarkers to predict success of immunotherapy treatments. The second year of the project will entail analysis of tissue samples collected from patients treated with different immunotherapies to determine whether and how B cell phenotypes correlate with clinical outcomes. MR: Melanoma is one of the most frequently diagnosed cancers among VA cancer patients, making it a serious healthcare burden.	*None to date*
CA160657 $670,000 Open	Lu/ Yale University	The Impact of Somatic Hematopoietic Mutations on Melanoma Tumorigenesis	RP: This study intends to 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. Thus far, the investigator has shown that loss of TET2 in hematopoietic cells results in smaller melanoma tumors. The PI will characterize cellular and molecular changes induced by TET2 loss in these models. MR: Health risks associated with military activities that entail exposure to ionizing radiation, carcinogens, and UV radiation will lead to genetic mutations in cells of various tissues. This project will examine whether mutations in tissue other than skin can regulate melanoma tumorigenesis.	*None to date*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
MELANOMA/SKIN CANCER				
CA160858 $543,335 Open	Cui/ University of New Mexico, Albuquerque	Development of Diagnostic Tools for Metastatic Melanoma via Imaging of Heparanase Activity	RP: Increased activity of the enzyme heparanase has been correlated with increased tumor metastasis and poor post-surgery survival. This project aims to develop new imaging tools to monitor tumor growth and metastasis by visualizing heparanase levels using positron emission tomography (PET) imaging. In the first year of the project, the investigator has developed synthetic molecular probes to monitor heparanase activity in melanoma cells. If successful, this project could inform new approaches to visualizing metastatic disease in patients. MR: Malignant melanoma is one of the most common cancers among Active Duty Service members, with approximately 2,000 Service members (mostly Caucasian) diagnosed between 2000 and 2011. Service members are usually discharged with melanoma if it has metastasized and they are limited in performance of their duties.	*None to date*
CA160896 $646,313 Open	Cantor/ Dana-Farber Cancer Institute	Immunotherapy of Melanoma: Targeting Helios in the Tumor Microenvironment for Effector Cell Conversion	RP: This study focuses on a specific transcription factor, Helios, which plays a role in the activity of suppressive regulatory T cells (Tregs). The investigator has demonstrated that inhibition of Helios signaling converts the T cells to have a genetic program more typical of effector T cells. The research team also demonstrated that Helios-expressing Tregs are localized in the tumor and lymph nodes, and that they also express the interleukin (IL)-23 receptor. Antibodies blocking IL-23R delay melanoma tumor growth and reduce the number of Tregs in the tumor. This suggests that IL-23R blocking antibodies are a potential candidate for immunotherapy in the treatment of melanoma. 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.	*None to date*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
MELANOMA/SKIN CANCER				
CA160997 $235,500 Open	Bajpai/ Stanford University	Investigating Epigenomic Reprogramming in Human Melanoma Development	RP: This study aims to identify early epigenetic events that drive the transformation of normal melanocytes into melanoma cells. The investigator is creating novel cell lines and using melanoma mouse models human melanoma samples to perform transcriptome and epigenomic analyses to elucidate the mechanisms behind the transformation process. This study will increase understanding of which genetic mutations drive the initiation of melanoma. MR: Military personnel and veterans belong to a 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.	*None to date*
CA170340 $644,000 Open	Xu/ University of Pennsylvania	Exosomal PD-L1 Mediates Tumor Immunosuppression	RP: Melanoma cells secrete vesicles called exosomes that express the inhibitory protein PD-L1. The investigators plan to determine the role of exosomal PD-L1 in inhibiting anti-tumor T cell function in melanoma, and whether the presence of the exosomes are a biomarker that predicts tumor burden and immune response in melanoma patients. MR: This study concerns a type of cancer related to UV radiation, an environmental carcinogen. Excessive sun exposure, which many military members endured over the last 15 years, induces 85 percent of all melanomas. In the near future, the PI expects that the incidence of melanoma (and other skin cancers) will drastically increase among Active Duty members and veterans.	*New research – no outcomes reported to date*
CA170374/P1/P2 $1,249,214 Open	Gershenwald; Davies; Tetzlaff/ The University of Texas MD Anderson Cancer Center	Integration of Clinical, Molecular, and Immune Features to Improve Risk Stratification and Outcomes in Melanoma Patients with Sentinel Lymph Node Metastasis	RP: This project intends to optimize and validate predictive clinical outcome models for Stage III melanoma patients to improve patient management strategies. MR: Melanoma is the second most common cancer diagnosis among U.S. Active Duty Service members.	*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				
CA170483/P1 $878,656 Open	Najjar; Delgoffe/ University of Pittsburgh	Metabolic Remodeling of the Tumor Microenvironment to Improve the Efficacy of Immunotherapy	RP: This study seeks to describe the effect of a novel combination therapy on immune cell function. The PI will obtain samples from a clinical trial enrolling melanoma patients, examine the effect of anti-PD1 therapy in combination with the type-2 diabetes drug metformin, and compare the immune cell characteristics of patients given the combination therapy with those given monotherapy. MR: Melanoma is the most commonly diagnosed cancer in the VA population.	*New research – no outcomes reported to date*
CA170628 $624,000 Open	Lombard/ University of Michigan, Ann Arbor	Targeting the Menin-MLL1 Interaction in Melanoma	RP: This project intends to investigate whether inhibitors to the scaffold protein Menin may prove efficacious as novel treatments for melanoma. The PI will examine the anti-cancer effect of the drugs on cell lines and in mouse models of melanoma. MR: Active Duty military personnel incur up to a 62 percent increased incidence of melanoma relative to the general population.	*New research – no outcomes reported to date*
CA170653 $688,000 Open	Smalley/ H. Lee Moffitt Cancer Center & Research Institute	Improving Therapy for Melanoma Brain Metastases	RP: This project aims to determine how the cross-talk between melanoma cells and the brain leads to changes at the molecular level that facilitate acquired resistance to therapy. The PI will use both mouse models of melanoma brain metastasis as well as patient samples to help describe these adaptive changes. MR: U.S. military personnel often operate under conditions of high UV exposure, one of the major environmental risk factors for melanoma development.	*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				
CA171012 $540,343 Open	Fallahi-Sichani/ University of Michigan, Ann Arbor	Defining and Targeting Novel Epigenetic Vulnerabilities in Heterogeneous Drug-Resistant Melanomas	RP: This study seeks to define the epigenetic states that contribute to kinase inhibitor resistance in melanoma. The PI aims to identify the key epigenetic regulators *in vitro* and validate their role in drug resistance *in vivo*. MR: Melanoma is the deadliest form of skin cancer, which has a higher incidence rate among Active Duty military personnel than in the general population, most likely due to Service members' longer exposure to UV ionizing radiation.	*New research – no outcomes reported to date*
CA171013 $476,000 Open	Ronai/ Sanford Burnham Prebys Medical Discovery Institute, La Jolla	Siah2 Ubiquitin Ligase in Immune Checkpoint and Melanomagenesis	RP: This project aims to characterize the role of Siah2, an ubiquitin ligase, in regulating the immune response to melanoma. Results from this project will identify (1) which immune cells are most affected by Siah2 loss, and (2) Siah2-dependent pathways critical for regulating immune cell function *in vitro* and *in vivo*. MR: There is an urgent need for effective melanoma treatments. This disease is highly relevant to military personnel given the key role of sunlight in the etiology of melanoma.	*New research – no outcomes reported to date*
CA171014 $594,000 Open	Yusuf/ University of Alabama at Birmingham	Pharmacological Management of Ultraviolet Radiation-Induced Skin Cancer	RP: This project intends to investigate the mechanism by which the Toll-like receptor-4 anatagonist TAK-242 regulates inflammation and prevents UV-induced oncogenesis. MR: Exposure to solar radiation and extremes of temperature and humidity contribute to the high prevalence of cutaneous disease among military personnel.	*New research – no outcomes reported to date*
CA171043 $648,923 Open	Hernando-Monge/ New York University School of Medicine	Identification of Glycomic Alterations During Melanoma Metastasis	RP: This project aims to identify glycosylation signatures that (1) promote melanoma brain metastasis, and (2) can be used as prognostic indicators of patient outcomes. MR: Melanoma incidence is increasing among military workforces deployed in regions with elevated sun exposure. Additionally, cutaneous tumors spread to other organs in about 30 percent of patients.	*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				
CA171056 $624,000 Open	Aplin/ Thomas Jefferson University	Optimizing Targeted Therapies for Wild-Type BRAF, Wild-Type NRAS (WT/WT) Melanoma	RP: This project seeks to identify the mechanisms of adaptive resistance to kinase inhibitor therapy in melanomas. Using *in vitro* single-cell approaches, as well as employing patient-derived cell organoids and xenograft models, the PI will investigate whether co-targeting multiple protein kinases could be a more effective therapeutic strategy. MR: As stated in the February 2017 Medical Surveillance Monthly Report, during the last 15 years of study (January 1, 2001 through December 31, 2015), the incidence of malignant melanoma among U.S. military personnel increased exponentially through the years of military service.	*New research – no outcomes reported to date*
CA171106 $550,980 Open	Bardhan/ Vanderbilt University	Multiplexed Immunomarker Screening to Enable Patient-Tailored Immunotherapies	RP: This study aims to develop imaging tools to measure PD-L1 and other biomarker expression within melanoma tumors. The PI will then examine if these imaging tools are able to predict immunotherapy sensitivity in mice based upon their biomarker status. MR: Accurate predictive tools to enable that the right patient receives the right therapy is a significant unmet clinical need.	*New research – no outcomes reported to date*
CA171123 $550,800 Open	Gaddameedhi/ Washington State University, Pullman	Harnessing the Circadian Clock to Alleviate Ionizing Radiation-Induced Toxicity During Melanoma Therapy	RP: This project intends to investigate whether a connection exists between circadian clock function and the effectiveness of radiation therapy. This study will use *in vitro* and *in vivo* models to determine whether active circadian rhythm has a protective role against the adverse effects of radiation treatment alone or in combination with immunotherapy. MR: The incidence of melanoma among Active Duty military personnel has been increasing, and now exceeds that of the general population.	*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				
CA171179 $622,002 Open	Jimeno/ University of Colorado at Denver	Modeling Neoantigen and TCR Dynamics in Melanoma and Its Role in Acquired Resistance to Immunotherapy Using Autologous Thymus-Bearing Humanized Mice	RP: This project aims to establish a benchmark for neoantigen content in melanoma tumors and to define patterns associated with innate and acquired resistance during the course of immune-directed therapy. MR: This study addresses the focus area of military-relevant etiologic factors and unmet gaps in the treatment of conditions, especially given that melanoma prevalence in the military population exceeds that of the civilian population.	*New research – no outcomes reported to date*
CA171198 $702,000 Open	Tinoco/ Sanford-Burnham Medical Research Institute, La Jolla	Targeting the PSGL-1 Immune Checkpoint to Promote Melanoma Tumor Control	RP: This study aims to investigate the role of P-selectin glycoprotein 1 (PSGL-1) signaling in anti-tumor T cell inhibition. The goal is to develop an immunotherapy to block PSGL-1, which will activate immune cells to target the tumor. The study plan entails deletion of PSGL-1 in mice to investigate how this receptor affects immune cell development and function. Second, this study will block PSGL-1 in mice to determine whether the T cells will control the tumor. MR: Rates of melanoma are higher among military members than in the general population, with the rate increasing among younger men in the military, particularly in the Air Force.	*New research – no outcomes reported to date*
CA180191 $1,783,047 Under Neg	Ertl/ Wistar Institute	Optimizing Active Immunotherapy of Melanoma Through Metabolic Reprogramming of Melanoma Antigen-Specific CD8+ T Cells Combined with Checkpoint Blockade	RP: The objective of this project is to improve treatment of metastatic melanoma by altering T cells to enhance their anti-tumor function. T cells in the tumor are often in an environment that makes them metabolically inactive. This project will test whether drugs can alter T cell metabolism to promote anti-tumor activity. MR: Military personnel, especially those serving in the Air Force and those serving in tropical or desert climates, are at increased risk of skin cancer due to increased sun exposure and lack of sufficient sun protection. Thus, improved treatment of late stage melanoma is of high relevance to Active Duty Service members and veterans.	*Research not yet initiated*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
MELANOMA/SKIN CANCER				
CA180698 $1,635,864 Under Neg	Shah/ Brigham and Women's Hospital	Stem Cell-Mediated Targeted Therapies for Metastatic Melanomas	RP: The goal of this project is to develop a therapeutic vaccine to treat brain metastatic melanomas. The investigator previously demonstrated (through a FY 2014 PRCRP award) the efficacy of using mesenchymal stem cells (MSC) expressing engineered herpes virus to specifically target metastatic cells in the brain. The new project will use a novel mouse model that better capitulates metastatic melanoma, and engineer the MSCs to also deliver immunotherapeutics and growth factors in order to improve the oncolytic capability of the vaccine. MR: Melanoma is of particular interest to the U.S. military, because Active Duty personnel are often required to be outside for prolonged periods. With thousands of U.S. Army, National Guard, Coast Guard, Air Force, and Marine personnel stationed in sun-intense locales, military Service members potentially face a long-term risk of melanoma.	*Research not yet initiated*
CA180825 $639,840 Under Neg	Qin/ The University of Texas MD Anderson Cancer Center	Targeting a Stress-Derived Immunosuppressive Adenosine Pathway in Tumors Resistant to Checkpoint Inhibitors	RP: This project will characterize a signaling pathway that promotes an immunosuppressive microenvironment in many tumor types. The investigator will utilize uveal melanoma and pancreatic tumor samples to evaluate the clinical relevance of this pathway. Pre-clinical animal models will be used to assess the ability of small molecular inhibitors to target this pathway and modulate the tumor microenvironment. MR: Uveal melanoma is a rare subtype of melanoma. Melanoma is of particular interest to the military due to the increased exposure of Active Duty Service members to UV radiation. Development of new immunotherapies will be beneficial for patients with tumors that have a low response rate to immunotherapy, such as CRC, pancreatic cancer, and glioblastoma, which affect Service members and their beneficiaries.	*Research not yet initiated*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
MELANOMA/SKIN CANCER				
CA181014 $612,000 Under Neg	Setaluri/ University of Wisconsin at Madison	A Microfluidic Method to Define the Role of Skin Microenvironment in Melanomagenesis	RP: This project will test the hypothesis that skin cells, like keratinocytes and fibroblasts, influence the development of melanoma. The investigator will use microfluidic methods to isolate populations of skin cells. Then, the impact of UV-exposed fibroblasts and keratinocytes on melanoma development will be assessed. MR: Tasks, such as long periods of training exercises for soldiers or sailors, can influence daily UV radiation exposure. Deployment of military personnel over the past decade in countries with near maximum annual averages of solar radiation potentially increases their risk of melanoma. During 2001-2015, rates of malignant melanoma diagnoses among U.S. military members increased exponentially in relation to years of active military service.	*Research not yet initiated*
CA181046/P1/P2 $1,587,434 Under Neg	Slingluff/ University of Virginia Gastman/ Cleveland Clinic Foundation Bullock/ University of Virginia	Enhanced Melanoma Vaccine Against Neoantigens and Shared Antigens by CD40 Activation and TLR Agonists	RP: This project is a Phase I clinical trial to test the safety, immunogenicity, and biological effects of a novel cancer vaccine regimen. Patients with resected Stage II-IV melanoma will be enrolled, and their response to the vaccine will be measured by characterizing the molecular aspects of the immune response in skin, blood, and lymph nodes. MR: This project will address current needs in treatment and prevention of melanoma that may aid in prolonging life and reducing morbidity for active and retired military. If this vaccine approach is effective, it will pave the way for further development of this approach that may enhance the quality of life of melanoma patients.	*Research not yet initiated*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
MELANOMA/SKIN CANCER				
CA181131 $606,600 Under Neg	Boland/ Massachusetts General Hospital	Genomic and Immunologic Correlates of Immunotherapy Response and Resistance via Longitudinal Tumor and Extracellular Vesicle (EV) Analysis	RP: This project will aim to understand why approximately 60 percent of metastatic melanoma patients do not respond to immunotherapy. The investigator will analyze tumor samples to identify therapeutic resistance mechanisms. MR: The majority of melanomas are induced by excessive sun exposure, which many Service members experience during deployment.	*Research not yet initiated*
CA181152 $576,000 Under Neg	Liu/ The University of Texas MD Anderson Cancer Center	Myeloid-Derived Suppressor Cells Expressing Myeloperoxidase Directly Inhibit Adaptive Immune Cells Limiting Immunotherapy in Melanoma	RP: The goal of this project is to understand the mechanisms that contribute to an immunosuppressive tumor microenvironment in melanoma. The investigator will focus on a type of immune cell called myeloid-derived suppressor cells to determine their role in response to immunotherapy treatments. MR: U.S. military personnel and veteran populations have an increased risk for developing melanoma due to deployments. Therefore, it is imperative to improve current treatment strategies.	*Research not yet initiated*
CA181311 $235,046 Under Neg	Ito/ Broad Institute	Identification of Paralog Dependencies and Resistance Mechanisms in Melanoma	RP: This project aims to (1) identify genetic interactions involved in cutaneous melanoma, and (2) investigate mechanisms of resistance to targeted therapies currently approved and used in melanoma treatment. The investigator has developed novel genetic screening tools to perform these studies. MR: Cutaneous melanoma represents one of the most aggressive and deadliest forms of melanomas. Recent studies reveal that U.S. military and veteran populations are at increased risk for melanoma, compared to the nonmilitary population.	*Research not yet initiated*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
MELANOMA/SKIN CANCER				
CA181329 $236,700 Under Neg	Zhu/ Georgia Tech Research Corporation	Development of Ultrasound-Guided Photoacoustic Imaging for Noninvasive Detection of Metastatic Lymph Nodes in Melanoma Patients	RP: The investigator will develop an advanced, clinically translatable, non-invasive diagnostic tool that integrates ultrasound and photoacoustic imaging to provide accurate assessments of lymph node metastases in real-time. Results of this project will therefore improve the detection and diagnosis of melanoma. MR: This project will improve diagnostic techniques for melanoma by enabling real-time detection for accurate and reliable cancer identification and thus, significantly decrease the waiting time for diagnosis results. This technique will therefore minimize anxiety for Service members and their family members waiting for a diagnosis, and enable earlier initiation of treatments.	*Research not yet initiated*
CA181347 $577,800 Under Neg	Garrett/ University of Cincinnati	ROS Exploitation to Increase Efficacy of RAF Pathway Inhibition in Melanoma	RP: This project aims to understand why melanoma patients develop resistance to BRAF and MEK inhibitors. Cell lines and patient derived xenograft mouse models will be used to identify new drugs that can be used in combination with BRAF/MEK inhibitors to improve patient outcomes. MR: Acquiring a few severe sunburns in the early years of life is a melanoma risk. Hence, acute sun exposure of young military personnel, especially those with fair skin and propensity to burn rather than tan, and who are deployed in areas with excessive sunny climates, such as Iraq and Afghanistan, are at a high risk for developing melanoma.	*Research not yet initiated*

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: This study seeks to identify novel genes whose mutations predispose individuals to malignant mesothelioma. Whole exome sequencing of malignant mesothelioma patients with a genetic history of cancer was performed to identify susceptibility variants. After identifying gene variants, the investigator decided to focus on the gene BLM, which has been shown to regulate DNA repair and apoptosis. Mutations leading to loss of BLM were discovered in two of the families studied. *In vitro* validation showed that silencing BLM in mesothelioma cell lines protects these cells from apoptosis after asbestos exposure, and promotes cellular transformation and foci formation. The next year of the project will entail reporting on long-term *in vivo* studies that examine mesothelioma development in BLM knockout mice. Results of this project will contribute to the development of novel screening tools for mesothelioma detection and targeted therapeutics to improve mesothelioma treatment. MR: The majority of U.S. veterans incurred exposure to asbestos at some point during their military service in shipyards and aircraft, among other sites. Indeed, malignant mesothelioma is disproportionally overrepresented in the military, as veterans account for nearly one-third of all malignant mesothelioma diagnoses.	*None to date*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
MESOTHELIOMA				
CA150300 $552,343 Open	Bertino/ University of Hawaii	Preclinical Development of TVAX: An Advanced Multiantigen Vaccine for Therapy and Prevention of Malignant Mesothelioma	RP: The investigator aims to develop a vaccine (Tvax) designed to activate antigen-specific T cells for multiple targets to produce stronger anti-cancer responses for mesothelioma tumors. Using a mouse model of malignant mesothelioma, T cell activation, tumor burden, and survival were assessed after vaccination with different versions of Tvax. Results demonstrated that peptide-based Tvax was the most effective in reducing mesothelioma tumor burden and improving survival. With these promising data, the investigators will focus on producing a human Tvax and evaluate its ability to activate human T cells. MR: The military (primarily the Navy) used more than 300 products containing asbestos (e.g., valves, brakes, gaskets, cements, adhesives, pipe coverings), making Navy veterans one of the most at-risk groups for developing asbestos-related malignant mesothelioma. In fact, estimates indicate that one out of every four malignant mesothelioma patients is a former Navy Service member or shipyard worker.	*Presentation: 1*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
MESOTHELIOMA				
CA150671/P1/ P2/P3/P4 $1,249,214 Open	Yang; Carbone/ University of Hawaii Pass/ New York University School of Medicine Kanodia/ Cedars-Sinai Medical Center Mak/ University Health Network, Toronto	HMGB1 and Its Isoforms as Biomarkers for Mineral Fiber Exposure and MM Detection	RP: This project is studying the role of HMGB1, a regulator of inflammatory response, in mesothelioma development. The investigators have developed HMGB1 knockout mouse models and are currently performing long-term studies 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 investigators are also developing mass spectrometry protocols to assess the utility of HMGB1 isoforms as biomarkers of mineral fiber exposure. MR: The military (primarily the Navy) used more than 300 products containing asbestos (e.g., valves, brakes, gaskets, cements, adhesives, pipe coverings), making Navy veterans one of the most at-risk groups for developing asbestos-related malignant mesothelioma. In fact, estimates indicate that one out of every four malignant mesothelioma patient is a former Navy Service member or shipyard worker. Naval veterans who served in the era from World War II to the Vietnam War hold the greatest risk of asbestos-induced malignant mesothelioma, as all Sailors and shipyard workers were exposed via navigation rooms, mess halls, and sleeping quarters where asbestos was used.	*None to date*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
MESOTHELIOMA				
CA160250 $622,000 Open	Heasley/ University of Colorado at Denver	Identifying TME-Derived Pathways for Cotargeting with FGFR1 in Mesothelioma	RP: This project is examining the molecular changes that occur between mesothelioma cells and the tumor microenvironment (TME) as a result of FGFR inhibition. In the first year, mesothelioma cell lines were treated with a FGFR inhibitor to identify transcriptional changes following inhibition of FGFR. The investigator has also performed synthetic lethal screens in the mesothelioma cell lines to identify pathways that interact with FGFR, thereby revealing potential drug targets that would be complementary to FGFR inhibition. With the *in vitro* studies nearly finalized, the next year will focus on *in vivo* experiments to identify TME-derived pathways that may serve as additional drug targets. MR: Evidence demonstrates that former U.S. military members, especially Navy veterans, are among those most affected by asbestos exposure. Overall, experts estimate that approximately 30 percent of all mesothelioma cases are diagnosed in veterans.	*None to date*
CA160891/P1 $1,491,517 779,375 Open	Harpole/ Duke University Bueno/ Brigham and Women's Hospital	Military Exposure-Related Pleural Mesothelioma: An Innovative Translational Approach to Inform Novel Molecular-Targeted Treatment Development	RP: Using a civilian and military population, the research team aims to redefine the classification of malignant pleural mesothelioma into biologically and prognostically distinct subgroups. From this work, the team hopes to develop treatment plans rationally designed around the specific diagnostic/prognostic biomarkers unique to the newly defined subtypes. 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.	*None to date*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
MESOTHELIOMA				
CA170299 $394,281 Open	Lake/ University of Western Australia	The MexTAg Collaborative Cross: Understanding Genetic Modifiers in Mesothelioma	RP: This study aims to identify genes that promote or protect against mesothelioma. The investigators will use a new mouse model that develops mesothelioma after exposure to asbestos. The investigators will study mesothelioma progression in these mice, identify the genes that are involved, and then use mesothelioma datasets to determine the human genetic equivalents. MR: U.S. veterans, who comprise 30 percent of mesothelioma deaths in the United States, incurred asbestos exposure while deployed in the Middle East.	*New research – no outcomes reported to date*
CA170319 $539,500 Open	Viapiano/ State University of New York Upstate Medical University	A Theranostic Antibody-Cytokine Reagent for Diagnosis and Multipronged Therapy of Malignant Mesothelioma	RP: This project seeks to develop a dual diagnostic and targeted therapeutic for malignant mesothelioma. The PI will engineer and characterize an IL2-conjugated anti-fibulin3 antibody for the ability to treat malignant mesothelioma *in vivo*. The PI will also generate a gadolinium-labeled version for detecting the tumor burden through magnetic resonance imaging (MRI). MR: Historical exposure to asbestos in U.S. military installations, vehicles, or combat zones during the 1960s through the 1990s, resulted in a much higher incidence of malignant mesothelioma among military veterans compared to the general population.	*New research – no outcomes reported to date*
CA170630 $638,739 Open	Adusumilli/ Memorial Sloan Kettering Cancer Center	Cell-Selective, Repetitive, Irreversible Electroporation to Augment Mesothelioma CAR T-Cell Therapy	RP: The PI previously developed CAR-T cells that target mesothelin, a protein that is overexpressed in mesothelioma cells. In this study, the research team will determine whether a technique called irreversible electroporation can help the anti-tumor T cells localize to the tumor site more efficiently. MR: U.S. veterans, who comprise 30 percent of mesothelioma deaths in the United States, incurred asbestos exposure while deployed in the Middle East.	*New research – no outcomes reported to date*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
MESOTHELIOMA				
CA180253 $525,200 Under Neg	Klein/ VA Medical Center, Minneapolis, MN	Precision Oncology-Based Therapeutic Targeting in Mesothelioma	RP: The objective of this project is to develop a precision oncology-based treatment strategy for mesothelioma. The PI plans to use genomic testing to identify the best combinations of drugs to target the cell cycle and other cancer survival pathways. MR: Mesothelioma is a highly fatal disease that can affect those exposed to asbestos, especially those who have been on Navy ships and/or involved in shipbuilding. It is also very likely that deployed troops will be exposed to significant amounts of asbestos in parts of the world where asbestos use is not regulated.	*Research not yet initiated*
CA180889/ CA180889 $1,795,282 Under Neg	Adusumilli/ Memorial Sloan Kettering Cancer Center Zauderer/ Memorial Sloan Kettering Cancer Center	Assessment of Endogenous and CAR T-Cell Immunity Following Anti-PD-1 Agent as a Transition Step to Phase 2 Combination Immunotherapy	RP: This project aims to generate an effective immunotherapy protocol to treat mesothelioma patients. The investigator will combine patient-derived immune cells engineered to attack tumors with therapeutics that boost the immune response. If successful, the results will inform the development of a clinical trial. MR: Veterans and Service members are at risk for asbestos exposure due to the nature of their deployments. There have been no FDA-approved therapeutics for mesothelioma since 2003.	*Research not yet initiated*
MYELOMA				
CA180496 $691,348 Under Neg	Nefedova/ Wistar Institute	Regulation of Myeloma Progression by Protein Citrullination	RP: This study will test the hypothesis that targeting PAD4 would enhance immune responses and delay progress of myeloma. MR: Service members and veterans are at risk for developing multiple myeloma. This study offers a novel approach for myeloma treatment to improve the outcomes of Service members and veterans with this disease.	*Research not yet initiated*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
MYELOMA				
CA180190/P1 $1,525,000 Under Neg	Zhan and Bishop/ University of Iowa	CD24 Tumor-Initiating Cell as a Novel Therapeutic Target in Myeloma	RP: This study will test the hypothesis that CD38+/CD45-/ CD24+ cells have tumor-initiating cell features. Such cell populations in myeloma patients predicts early relapse in myeloma. MR: Myeloma is one of the common cancers among veterans. This project could lead to early detection and treatment, if its results identify a marker for disease development.	*Research not yet initiated*
MYELOPROLIFERATIVE DISORDERS				
CA150085 $551,362 Open	Felices/ University of Minnesota Twin Cities	Enhancing Natural Killer Cell Mediated Targeting and Responses to Myeloid Leukemias	RP: The study aims to enhance the immunotherapeutic value of natural killer (NK) cells against myeloid leukemia. The approach is to create TriKEs that target NK cells to myeloid tumor cells. MR: Exposure to ionizing radiation, chemicals, and other agents during deployment increases the incidence of myeloid malignancies. Novel therapeutic reagents that target myeloid malignancies are needed to help Warfighters combat these diseases.	*Publications: 4*
CA150493 $556,200 Open	Fleischman/ University of California Irvine	Inflammation as a Driver of Clonal Evolution in Myeloproliferative Neoplasm	RP: This study seeks 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 incurred radiation or chemical exposures during their military Service.	*Publications: 2* *Presentations: 12*
CA150529 $691,744 Open	Fraenkel/ Beth Israel Deaconess Medical Center, Boston	Discovering New Drug Targets in Radiation-Induced Myeloproliferative Neoplasms	RP: This study intends to perform the first systematic evaluation of genetic alterations in patients with MPN and previous exposure to ionizing radiation. MR: Service members have increased exposure to ionizing radiation, which causes bone marrow damage. This study will lead to new drug targets for radiation-induced MPNs.	*Publication: 1*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
NEUROBLASTOMA (NB)				
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 of this study is to develop novel therapeutic options for patients with high-risk NB based on disrupting the oncogenic functions of deregulated MYCN, either at the mRNA and/or the protein level. The PIs have developed and are testing the clinical applicability of the first-in-class CDK7-selective inhibitor, YKL-124. The long-term goal is to develop a compound that will produce durable responses in patients with MYCN-amplified NB. MR: NB accounts for nearly 15 percent of all deaths due to childhood cancer. Although the diagnosis and treatment of NB exact a heavy emotional and financial toll on all families, the impact is likely to be greater in military families, which often include one or more Active Duty Service members. The stresses imposed by prolonged hospital admissions for intensive treatment or its complications, and the need to travel far from home to seek specialized care and experimental treatments following relapse, cannot be overemphasized.	*None to date*
CA160360 $556,500 Open	Zhu/ Mayo Clinic and Foundation, Rochester	Understanding the Cooperation Between LMO1 and MYCN in Neuroblastoma Metastasis Using a Novel Zebrafish Model	RP: The PI will use a validated zebrafish model of NB metastasis, combined with state-of-the-art live imaging, tumor cell transplantation, CRISPR-cas9-mediated genome editing, and a novel tissue-specific, conditional doxycycline-regulated system, to identify key pathways downstream of the oncogene, LMO1, which interact with a second oncogene, MYCN, in NB metastasis. So far, the PI has demonstrated that members of the lysyl oxidase (LOX) family are critical for LMO1-mediated NB metastasis. MR: NB is the most common extracranial solid tumor of childhood, accounting for about 10 percent of all cancer-related deaths among children. The development of NB among 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.	*Publication: 1*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
NEUROBLASTOMA (NB)				
CA170257/P1 $1,702,500 Open	Hogarty; Asgharzadeh/ Children's Hospital, Philadelphia	Altering the Tumor Microenvironment to Augment Neuroblastoma Immunotherapy	RP: The goal of this project is to test the hypothesis that the solid tumor microenvironment (TME) is a byproduct of the specific oncogenes driving the cancer, and that NBs with different driver mutations will have distinct immunosuppressive TMEs. MR: Children of military personnel are often affected, as NB is the most common childhood solid tumor, and the stress associated with having a critically ill child negatively impacts the military readiness of Armed Forces.	*New research - no outcomes reported to date*
CA171026 $606,661 Open	Freeman/ St. Jude Children's Research Hospital	Investigating the Downstream Oncogenic Consequences and Therapeutic Susceptibilities Caused by Loss of ARID1A in Neuroblastoma	RP: The PI will test the hypothesis that ARID1A is a predominant 1p36 tumor suppressor, whose loss relieves N-Myc induced replication stress in NB, and that loss of ARID1A via 1p36 deletion in a model of NB will recapitulate the drug sensitivities of ARID1A mutated cancers. MR: The military-relevant focus of this proposal is to advance better treatment for NB patients who are dependents of military personnel and veterans.	*New research - no outcomes reported to date*
CA180461 $640,361 Under Neg	Barbieri/ Baylor College of Medicine	MYCN Reprograms Neuroblastoma Metabolism	RP: The overall objective of this project is to determine how MYCN contributes to NB tumorigenesis through activation of lipid metabolism. MR: Novel targeted approaches are urgently needed for this highly aggressive malignancy, which, in spite of our best efforts, has poor survival rates upon disease relapse. The possibility of developing more targeted and less toxic therapies is necessary to alleviate the hardship these military families endure when a child is diagnosed with NB.	*Research not yet initiated*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
NEUROBLASTOMA (NB)				
CA180793 $601,791 Under Neg	Cripe/ Research Institute at Nationwide Children's Hospital	BiTE Gene Therapy to Augment Oncolytic Virotherapy	RP: The PI will test the hypothesis that intratumoral anti-viral T cells resulting from oncolytic virotherapy can be redirected to cancer cells by sustained systemic expression of a secreted bi-specific T cell engager. MR: The diagnosis of cancer in a military member, veteran, or their children negatively impacts the military, as it cripples a family, both financially and emotionally. By improving cancer therapies with fewer side effects, the PI hopes to reduce the burden of cancer on the military families.	*Research not yet initiated*
CA181419 $240,939 Under Neg	Mukherjee/ University of California, San Francisco	Drugging the Aurora Kinase A Interactome in Neuroblastoma	RP: The PI will test the hypothesis that the activity state of the mitotic protein, AURKA, stabilizes the oncoproteins, MYC and MYCN, and that defining members of the activity state-dependent interactome and mechanisms of resistance to the conformation disrupting molecule, CD532, will clarify underlying NB biology and illuminate how conformation disrupting inhibitors of AURKA drive degradation of MYC proteins. MR: Successful completion of this project would not only define the mechanism of action of CD532, but also identify novel therapeutic targets directly applicable to the clinic, and would have a vast impact on Service members' families affected by a NB diagnosis.	*Research not yet initiated*

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. In this study, 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 enable those T cells infiltrate the pancreatic tumor and cause tumor rejection. MR: Exposure to pesticides used in Vietnam, such as DDT, 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 the immune system can target, correlate with the success rate of immunotherapy.	*None 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 study is to determine the prevalence of somatic mosaicism for cancer predisposition genes, gleaned from normal tissues of patients with pancreatic cancer. MR: In the military population, links between environmental exposures, such as AO, and increased incidence of a variety of malignancies and known cancer syndromes, may affect the ability of an individual to serve effectively. Somatic mosaicism may provide an alternative and more probable explanation for cancers occurring among young men and women currently serving or who may have served in the military, rather than a presumed link to a military occupational exposure.	*None 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 $1,567,577 POPEX	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 study aims to test 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 investigators 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 this study will enable them to develop a novel combination regimen for Active Duty or veteran personnel with pancreatic ductal adenocarcinoma, which will enable a meaningful, rather than a statistical, improvement in survival.	*Publication: 1*
CA160097 $702,000 Open	Commisso/ Sanford-Burnham Medical Research Institute, La Jolla	NHE7 as a Novel Drug Target in Pancreatic Cancer	RP: In this study, 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 research could lead to the development of new treatment paradigms within the MHS in the near future.	*None to date*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
PANCREATIC CANCER				
CA160269 $588,346 Open	Lynch/ Institute for Cancer Research	Towards Precision Prevention: Testing a Novel Risk Prediction Algorithm in Pancreatic Cancer	RP: In this study, 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 1,400 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 (e.g., 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 from pancreatic cancer than are 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.	*None to date*
CA160311 $552,600 Open	Dudeja/ University of Miami	Effect of HSP70 in Immune Environment on Pancreatic Cancer Growth	RP: In this study, 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, since the U.S. veteran population, by virtue of increased excessive use of tobacco and alcohol, is more prone to pancreatic cancer.	*None to date*

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 PDAC cells. Also, the PI plans to determine the downstream consequences of Lin28b activation in this subset of pancreatic cancers, and to 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).	*Publications: 2*
CA160771 $617,542 Open	Yu/ Emory University	Improving Pancreatic Cancer Therapy Through Understanding and Exploiting SAMHD1 in DNA Repair	RP: The objective of this study 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 genotoxic agent exposures, such as ionizing radiation and environmental carcinogens. Improved treatment approaches would have a particularly profound impact on military members because pancreatic cancer is disproportionally represented in the military.	*Presentations: 2* *Publication: 1*
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 Ca^{2+}-CaM may lead to the development of novel anti-cancer therapeutics.	*Presentation: 1*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
PANCREATIC CANCER				
CA161010 $232,500 Open	Purohit/ New York University	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 (PDAC). MR: Completion of these studies will greatly improve our understanding of PDAC biology and uncover novel therapeutic targets beneficial to everyone, including Service members, veterans, and their families.	*Presentation: 1*
CA170314 $620,000 Open	Mo/ University of Mississippi Medical Center	Identification of lncRNAs Required for Synthetic Lethal Interactions with Mutant KRAS in Pancreatic Cancer	RP: The PI hypothesizes the long non-coding RNAs (lncRNAs) play an important role in regulating the RAS pathway. The goal of this project is to identify these regulatory lncRNAs and determine their role in pancreatic cancer pathogenesis. MR: The success of this study will have a great impact on pancreatic cancer diagnosis and therapy, and will thus benefit those who suffer from this devastating disease, especially military personnel.	*New research – no outcomes reported to date*
CA170450 $678,000 Open	Miller/ New York University School of Medicine	Investigating the Role of Piezo1 in Pancreatic Cancer-Related Immune Suppression and Disease Progression	RP: The PI will study the role of a mechanosensitive ion channel (Piezo1) in promoting immune tolerance, and thus tumor growth, in PDAC. He will also test whether inhibiting Piezo1 enables efficacy of checkpoint-based immunotherapy in PDAC. MR: PDAC is the third leading cause of cancer-related death in the United States; there are few long-term survivors. Several studies have found an increased risk of pancreatic cancer among veterans who deployed overseas during the Vietnam War. Additionally, veterans with diabetes are particularly at increased risk of developing pancreatic cancer.	*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				
CA170568 $490,258 Open	Fridman/ Wayne State University	Disrupting Collagen-Mediated Prosurvival Pathways in Pancreatic Cancer	RP: In this study, the PI will assess the role of Discoidin Doman Receptor (DDR) kinases, major family of collagen receptors, in mediating resistance of pancreatic tumors to MEK inhibition. The PI will test the hypothesis that disrupting DDR function by pharmacological or genetic means may attenuate PDAC pro-survival/fibrotic pathways and enhance therapeutic efficacy drugs targeting Kras-driven (MEK) signaling networks. MR: Two major risk behaviors associated with developing pancreatic cancer (i.e., smoking and alcohol abuse) are observed more often among military members with combat experience than in the public.	*New research – no outcomes reported to date*
CA170974/P1/P2 $1,721,374 Open	Chung; Pandol/ Cedars-Sinai Medical Center Tomlinson/ University of California, Los Angeles	Sensitization of Therapeutic-Resistant Pancreatic Cancer by Cancer Cell-Specific Drug Delivery	RP: This study will (1) assess whether a pancreatic tumor-specific drug, heptamethine carbocyanine and simvastatin (HMCD-SIM), can resensitize PDAC tumors to chemotherapy; and (2) determine the mechanisms of action for HMCD-SIM. This study will also assess the use of G protein coupled receptor-associated sorting protein 1 (GASP-1) as a biomarker for early detection of PDAC. MR: The combination of the poor prognosis of pancreatic cancer (only a seven percent five-year survival rate) and increasing evidence indicating that military service elevates pancreatic cancer risk, results in an increased burden to the MHS.	*New research – no outcomes reported to date*
CA171001 $554,400 Open	Sherman/ Oregon Health & Science University	Understanding Stromal Fibroblast Heterogeneity in the Pancreatic Tumor Microenvironment	RP: In this study, the PI will assess the contribution of pancreatic stellate cell (PSCs) to the PDAC microenvironment, analyze the interactions between PSC-derived cancer-associated fibroblasts (CAFs) and PDAC cells, and understand the significance of PSC homeostasis during PDAC progression. MR: Veterans are at increased risk of developing pancreatic cancer due, in part, to the associations between alcohol use and pancreatic cancer risk, and between diabetes and pancreatic cancer risk.	*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				
CA180325/P1/P2 $1,651,000 Under Neg	Miller/ New York University School of Medicine Cohen/ New York University School of Medicine Saxena/ New York University	Targeting the Microbiome to Enable Immunotherapeutic Efficacy in Pancreatic Carcinoma	RP: The goal of this study is to identify specific bacterial species and combinations associated with immunogenic activation of the PDAC tumor microenvironment. The PI will test the efficacy of the identified antibiotic and probiotic regimens on tumor immunity in animal and human PDAC models, and eventually, test the safety and efficacy of bacterial ablation in combination with αPD-1 treatment in PDAC patients. MR: Military personnel and veterans are at increased risk of developing PDAC. Treatment options are limited, resulting in poor prognosis. Results from this study could provide a novel treatment strategy aimed at targeting the tumor microbiome.	*Research not yet initiated*
CA180514 $669,999 Under Neg	Gorelick/ Yale University	The Survival Factor Renalase and Pancreatic Cancer	RP: Renalase (RNLS) is a secretory protein that promotes growth of cancerous tissue, and was found to be elevated in pancreatic cancer (i.e., PDAC) tissues. This study will investigate the biological characteristics of different RNLS-protein complexes, determine which form of RNLS is secreted from tumor cells, and perform studies to determine levels and distribution in cancerous tissues. MR: Pancreatic cancer is the deadliest common cancer, and has a higher prevalence in the veteran population. This study will provide information on whether RNLS can be used to stage pancreatic cancer and predict prognosis.	*Research not yet initiated*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
PANCREATIC CANCER				
CA180759 $158,5000 Under Neg	Chen/ Baylor College of Medicine	Noncanonical Function and Regulation of the Unfolded Protein Response in Mutant KRAS-Driven Pancreatic Ductal Adenocarcinoma	RP: The goals of this study are to establish the biological significance and molecular mechanisms of activation of the UPR pathway by mutant KRAS, and to develop a novel and effective mechanism-based therapy for PDAC patients. MR: Military personnel are at increased risk of PDAC due to pancreatic cancer risk factors associated with occupational exposures. Results from this study could provide a new treatment option by targeting common mechanisms downstream of KRAS effector pathways.	*Research not yet initiated*
CA181275 $228,750 Under Neg	Yang/ University of Texas Health Science Center at San Antonio	Glutamine-Mediated Tumor-Stromal Interaction: A Novel Target for Pancreatic Cancer Treatment	RP: The PI hypothesizes that glutamine-mediated signaling (1) promotes PSC-pancreatic cancer cell (PCC) communication; (2) causes increased survival of PDAC cells; and (3) that palmatine (PMT), a small molecule, can disrupt this communication and improve response to therapeutics. The PI will determine the mechanism through which glutamine mediates PSC-PCC communication to promote cancer survival and proliferation, as well as the ability of PMT to inhibit this process. This study will also determine the efficacy of PMT-mediated glutamine inhibition to improve response to conventional therapeutics. MR: Military personnel and veterans are at increased risk of developing PDAC. Results from this study could identify a new molecule for better management of PDAC, and provide mechanistic knowledge on glutamine-mediated PSC-PCC communication and therapeutic resistance.	*Research not yet initiated*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
PANCREATIC CANCER				
CA181504 $559,799 Under Neg	Pylayeva-Gupta/ University of North Carolina at Chapel Hill	Role of IL-23 in Epithelial-to-Mesenchymal Conversion in Pancreatic Cancer	RP: The PI will test the hypothesis that expression of IL-23 by myeloid cells suppresses EMT conversion of pancreatic cancer (i.e., PDAC) cells, thus limiting their metastatic potential. The PI will determine how cytokine IL-23 promotes metastasis of PDAC, and will explore the potential of this pathway as a prognostic and therapeutic target. MR: Pancreatic cancer is a deadly disease with increased rates among military personnel. Results from the proposed studies will provide mechanistic insight into PDAC metastasis, as well as the therapeutic potential of IL-23.	*Research not yet initiated*
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: In this study, the PI will test the hypothesis that the chloride channel CLIC1 is a medulloblastoma (MB)-specific regulator and potential therapeutic target. Data thus far demonstrate that Clic1 knockout reduced MB tumor burden, reduced tumor-associated hydrocephalus and cranium bulging, and significantly extended the survival of tumor-bearing mice. Investigation into the mechanism of these observations suggests that Clic1 specifically regulates the proliferation of the rapidly dividing tumor progenitor cells, but not the slow cycling Sox2+ cells. 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 his or her duties, thus decreasing the readiness of our military.	*None to date*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
PEDIATRIC BRAIN TUMOR				
CA160373 $677,999 Open	Law/ Cornell University, Weill Medical College	Multifunctional Nanofiber for Convection-Enhanced Delivery of Theranostics to Diffuse Intrinsic Pontine Glioma	RP: In this study, the PI and his collaborators are formulating a peptide nanofiber (NFP) to carry a drug cocktail (panobinostat and GSK-J4) directly to diffuse intrinsic pontine glioma (DIPG) tumors via convection-enhanced delivery. 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. Families of Active Duty Service members already suffer from long-distance relationships. A DIPG diagnosis of a child puts the entire family into a stressful, desperate, and helpless position.	*Publication: 1*
CA160414 $549,000 Open	Sayour/ University of Florida	RNA-Nanoparticles Targeting H3.3 K27M Epitopes in Diffuse Intrinsic Pontine Glioma	RP: In this study, the PI will use preclinical models of DIPG to test the hypothesis that lysosomal associated membrane proteins (LAMP) conjugated with RNA nanoparticles (RNA-NPs) targeting neoantigens will enhance major histocompatibility complex class II (MHC II) presentation and potentiate anti-DIPG activity. Preliminary data demonstrate the feasibility and immunologic activity of generating RNA-NPs that target the H3.3K27M mutation based on MHC prediction binding algorithms. The data also demonstrate that this prediction may be essential for enhancing immunologic memory to confer long-standing anti-tumor immunity in a personalized fashion for DIPG patients, without the need for intratumoral resection. MR: The ability to select therapeutic strategies with greater likelihood to be effective against individual tumors without toxicity, as proposed in this application, will have a dramatic impact on civilians, military personnel, and their families.	*Publication: 1* *Presentations: 2*

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: This study aims to develop improved tumor-targeted oncolytic adenoviruses to treat diffuse intrinsic pontine gliomas. The investigators will first assess the activation, proliferation, and development of memory cell tumor infiltrates in tumor samples collected from a complete adult glioma clinical trial. They will then perform preclinical studies in immunocompetent models of DIPG to develop improved viruses, with the aim of improving immune cell response in DIPG. Preliminary analyses of the adult trial data indicate that virotherapy might be responsible for increased lymphocyte presence within the tumor, and that it modifies the expression of immune checkpoints (e.g., TIM3, a co-inhibitory receptor). MR: To date, DIPG is an incurable disease that adversely affects the preparedness of our military.	*None to date*
CA160704 $559,800 Open	Venkataraman/ University of Colorado at Denver	Dependency of H3K27M-Mutated DIPG on BMI1-Mediated Cell Self-Renewal	RP: In this study, the PI proposes investigating the role of BMI1 in enhancing DIPG tumor growth, and intends to identify the molecular consequence of H3K27 mutation with BMI1 in triggering cancer stem cell proliferation. To date, the PI has found that genetic knockdown of BMI1 or pharmacological treatment to inhibit BMI1 function can cause resistance to BMI1 inhibition. This is due to increased expression of anti-apoptotic proteins that protects the cells from treatment. Inhibiting these anti-apoptotic proteins after BMI1 inhibition prevents the acquired resistance to BMI1 inhibition and increased cell death. MR: Improving pediatric patient care will allow Service members to return quickly to military service, as the time needed for intensive care of their dependents will be decreased, enabling them to balance the needs of their families with the needs of their service.	*None to date*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
PEDIATRIC BRAIN TUMOR				
CA160916 $262,500 Open	Panditharatna/ Children's Research Institute	Preclinical Precision Targeting of Major Driver Mutations in Childhood Diffuse Intrinsic Pontine Glioma	RP: In this study, 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 DIPG. MR: DIPG is a deadly pediatric brain tumor that affects about 200-300 families every year in the United States, including numerous military families.	*New research – no outcomes reported to date*
CA170414 $536,431 Open	Mulcahy; Levy/ University of Colorado at Denver	Optimization of Autophagy Inhibition as a Clinical Target for Brain Tumors	RP: In this study, the PI will define how and why autophagy inhibition is effective in RAF pathway-driven central nervous system (CNS) tumors; how best to inhibit the pathway; and what additional biomarkers might be available for autophagy dependence to plan effective future autophagy inhibition trials and improve the survival of CNS tumor patients. MR: RAF pathway-driven CNS tumors affect children, adolescents, and adults. Improving the care of these patients will enable Service members to more rapidly return to service, as the time needed for intensive care for themselves or their dependents will be decreased, enabling them to balance the needs of their families with the needs of their service.	*New research – no outcomes reported to date*
CA170677 $622,000 Open	Vibhakar/ University of Colorado at Denver	SIRT2 as an Epigenetic Vulnerability in Atypical Teratoid Rhabdoid Tumors	RP: The goals of this project are to determine the molecular mechanisms by which the deacetylase SIRT2 drives atypical teratoid rhabdoid tumor (ATRT) formation, and to provide preclinical validation of SIRT2 inhibition as a therapeutic approach in treating ATRT. MR: ATRT is an aggressive and malignant pediatric brain tumor. Current therapies are not optimal and leave children with many long-term side effects. These issues require significant resources and family time. Improving the care of pediatric patients will allow Service members to return quickly to military service, as the time needed for intensive care of their dependents will be decreased.	*New research – no outcomes reported to date*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
PEDIATRIC BRAIN TUMOR				
CA170822 $655,000 Open	Raabe/ Johns Hopkins University	Targeting Abnormal Epigenetics in Diffuse Intrinsic Pontine Glioma by Inhibiting TET Enzymes	RP: In this study, the PI will test the hypothesis that inhibition of TET enzymes will lead to reduced levels of the epigenetic modification 5hmC; restored epigenetic balance; decreased tumorigenicity; and increased sensitivity to radiation and chemotherapy. MR: The preponderance of young people and parents in Active Duty military service means that pediatric and young adult brain tumors have a disproportionate impact on the health and well-being of military Service members and their dependents. Diffuse midline gliomas, including diffuse intrinsic pontine glioma (DIPG), largely affect children and young adults, and have a 100 percent mortality rate.	*New research – no outcomes reported to date*
CA171021 $589,500 Open	Rubens/ Johns Hopkins University	Targeting Oncoprotein-Adapted Amino Acid Metabolism in Atypical Teratoid Rhabdoid Tumors	RP: In this study, the PI will test the hypothesis that the transcriptional regulator MYC drives adaptations in amino acid metabolism that can be pharmacologically targeted to improve survival in ATRT, a form of malignant brain tumors diagnosed in infancy. MR: Childhood cancer disproportionately affects military personnel and their families, but is grossly underrepresented in government supported research. A Service member coping with a child being treated for ATRT, which only has a median survival of 6-11 months, negatively impacts mission readiness.	*New research – no outcomes reported to date*
CA171067 $577,611 Open	Thompson/ Duke University	The Role of CD155 in Leptomeningeal Dissemination and Oncolytic Virus Susceptibility in the Medulloblastoma Microenvironment	RP: In this study, the PI will test the hypothesis that the oncolytic polio viral immunotherapy (PVSRIPO) will infect both solid tumor and metastatic leptomeningeal medulloblastoma (MB) cells *in vivo*, resulting in tumor cell killing and an ensuing innate and durable adaptive immune response. MR: Children of a parent who served in the Air Force are at increased brain tumor risk. Brain cancer, such as MB, in a Warfighter or in a Warfighter's child can interfere with mission readiness.	*New research – no outcomes reported to date*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
PEDIATRIC BRAIN TUMOR				
CA171070 $620,000 Open	Hinchcliffe/ University of Minnesota Twin Cities	Cellular Mechanisms Underlying Pediatric Glioblastoma: Heterozygous Mutations in Histone H3.3 Induce Chromosome Instability by Abolishing Ser31 Phosphorylation	RP: In this study, the PI will test the hypothesis that mutations in the N-terminal tail of histone H3 variant H3.3 deplete H3.3 phosphorylation on the amino acid Ser31, thereby inducing chromosome instability during cellular division. The resulting daughter cells are then susceptible to increasing rates of mutation because of their unbalanced genomes. MR: Pediatric brain cancer has a higher incidence in the military population. The high-grade gliomas associated with our research are caused by somatic mutation, which are often caused by exposure to environmental toxins (and themselves risk factors) associated with military service.	*New research – no outcomes reported to date*
CA171185 $577,200 Open	Phoenix/ University of Cincinnati	Defining and Targeting the Blood-Brain Barrier in Pediatric Glioma Subgroups	RP: This study aims to take an unbiased approach to define BBB function across pediatric glioma subgroups, and determine whether suppression of DIPG Wnt signaling will alter BBB function and improve drug efficacy. MR: Alterations in brain vasculature play an important role in neurological diseases, including brain tumors, stroke, head trauma, and neurodegenerative disorders. This research will advance our understanding of brain blood vessel properties and their dysfunction during disease, directly impacting Service members and their families.	*New research – no outcomes reported to date*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
PEDIATRIC BRAIN TUMOR				
CA180395 $655,000 Under Neg	Raabe/ Johns Hopkins University	Targeting LIN28 in Pediatric Brain Tumors Using Circular RNA Decoys	RP: In this study, the PI will test the hypothesis that a specific circular RNA molecule will function as a sink to consume the stem cell reprogramming factors LIN28A and LIN28B, resulting in the death of LIN28-dependent brain tumor cells. The PI will also study whether synthetic RNA molecules can be packaged in extracellular vesicles, delivered to pediatric brain tumor cells, and arrest tumor growth. MR: More than half of Active Duty military Service members are less than 25 years of age, and one in three Active Duty Service members has children. Therefore, there is a desperate need for new, innovative approaches to treat ATRT, DIPG, and glioblastomas (GBM). Such a therapy, as will be studied in this proposal, will significantly reduce the burden of disease affecting the military population and their beneficiaries, thus improving mission readiness.	*Research not yet initiated*
CA181015/P1/P2 $1,611,169 Under Neg	Diaz/ University of California, San Francisco Kasahara/ University of California, San Francisco Mueller/ University of California, San Francisco	Oncolytic Viral Therapy to Potentiate Immune Checkpoint Blockade in Immunologically Cold Brain Tumors	RP: The objective of this project is to evaluate the interactions of the measles virus (MV-NIS) and the retrovirus Toca 511 with the endogenous anti-MB immune response, as monotherapies and in combination with immune-checkpoint blockade. The team expects that oncolytic virus (OV) therapy accelerates T-cell killing of MB cells *in vivo*, and that this is enhanced by immune-checkpoint inhibition. MR: The preponderance of young people and parents in Active Duty military service means that pediatric, adolescent, and young adult brain tumors have a particularly profound impact on the health and well-being of military Service members. Outcomes of this research will enable risk stratification for existing patients receiving MV-NIS therapy, and will provide a rationale for future trials combining OV and immune-checkpoint inhibition, which would profoundly affect the negative impact of a MB diagnosis on mission readiness.	*Research not yet initiated*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
PEDIATRIC BRAIN TUMOR				
CA181154 $260,925 Under Neg	Straehla/ Massachusetts Institute of Technology	Targeted, Rationally Designed Nanoparticle Therapeutics for Pediatric Medulloblastoma	RP: In this study, the PI will develop a multi-layered nanoparticle to treat pediatric MB. The nanoparticles will be designed to be shuttled across the BBB, rather than having to cross the BBB through passive diffusion. If successful, the proposed work opens the door for exciting therapeutic advances in pediatric MB, as the platform is extremely versatile and nearly any therapeutic compound could be loaded into the nanoparticle core. MR: This work is highly relevant to Service members, veterans, and their families, since the PI undertakes an urgent unmet need – targeted drug delivery through the BBB for the treatment of pediatric brain tumors.	*Research not yet initiated*
STOMACH CANCER				
CA150079 $586,758 Open	Bass/ Dana-Farber Cancer Institute	Developing Mouse Models of Stomach Cancer with CRISPR/Cas9 Technologies and Environmental Exposures	RP: This study aims to develop a mouse model for stomach cancer using CRISP/Cas9 technology. MR: Service members are exposed to infectious and chemical agents that increase the risk of stomach cancer. This study seeks to develop technologies that lead to better understanding and treatment of stomach cancer.	*Funding Obtained: 9*
CA150132 $396,000 Open	Gough/ Monash University	Defining the Efficacy of Blocking Serine Phosphorylated STAT3 in the Treatment of Gastric Cancer	RP: This study seeks to test the hypothesis that targeting mitochondrial pS727 STAT3 will suppress inflammation associated tumorigenesis. MR: Service members have a higher rate of *H. pylori* infection than do 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.	*Publications: 7*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
STOMACH CANCER				
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 and pathways for gastric cancer by analyzing Pan-GI data. MR: Service members are at increased risk of developing stomach cancer when deployed to regions with higher rate of *H. pylori* infection. This study will expand our knowledge of gastric cancer and could potentially improve treatment options for the military.	*Publication: 1* *Presentation: 1*
CA150334 $640,000 Open	Ajani/ University of Texas MD Anderson Cancer Center	Exploiting RhoA Mutations in Diffuse Gastric Adenocarcinoma and Targeting Intertwined RhoA and Yap1 Pathways for Therapeutic Advantage	RP: This study intends to test the hypothesis that RhoA and Yap1 pathways are novel targets for diffuse gastric adenocarcinoma (dGAC), and that the dual inhibition will provide added advantage against dGAC. MR: Service members are at increased risk of developing stomach cancer when deployed to regions with higher rate of *H. pylori* infection. This study could lead to new treatment options for stomach cancer.	*None to date*
CA150375 $607,557 Open	Reyes/ University of Texas Medical Branch Galveston	Molecular Characterization of *H. pylori* Strains and Biomarkers in Gastric Cancer	RP: This study aims to understand the genetic features of *H. pylori* strains linked to stomach cancer; and to identify biomarkers for stomach cancer. MR: Service members deployed to regions with higher *H. pylori* prevalence are at risk for *H. pylori* infection and stomach cancer, one of the most common cancers treated in the VA system.	*None to date*
CA150646/P1/P2 $1,322,311 Open	Janjigian; Lewis/ Memorial Sloan Kettering Cancer Center Tavazoie/ Rockefeller University	89Zr-Trastuzumab-PET, Rapid Autopsies, and Patient-Derived Xenografts to Determine the Extent of Clonal Evolution in Treatment-Refractory HER2+ Gastric Cancer	RP: This study aims to understand the mechanism of drug resistance in esophagogastric cancer (EG). The hypothesis is that HER2 levels between primary tumor and metastasis sites may contribute to the drug resistance. Furthermore, mutation of key kinases and deregulated expression of small non-coding RNAs (miRNAs) contribute to drug resistance in HER2-positive EG. MR: EG cancer is increasing rapidly and highly impacts the military and veteran populations.	*Publications: 3*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
STOMACH CANCER				
CA150647/P1/ P2/P3/P4 $1,535,985 Open	Korn; Collisson; Fong; Ashworth/ University of California San Francisco Janjigian/ Memorial Sloan Kettering Cancer Center	Targeting BRCAness in Gastric Cancer	RP: This study intends to test a combination therapy using immunotherapy and PARP inhibition to treat gastric cancers displaying BRCAness. MR: Service members incur higher risks of *H. pylori* infection and radiation exposures, resulting in increased risk of gastric cancer development.	*None to date*
CA150742 $89,700 Open	Sung/ National Cancer Institute	Discovery and Validation of Plasma DNA Methylation Biomarker for Detection of Stomach Cancer	RP: This study aims to identify and validate plasma DNA methylation as a potential biomarker for the detection of stomach cancer. It will use blood samples from patients and case-control subjects to identify and test biomarker utility. MR: If shown to be valid, these biomarkers, based on a simple blood test, have the potential to transform stomach cancer screening and reduce disease-related mortality in the public and in military members, veterans, and their families.	*None to date*
CA150895 $131,250 POP EXP	Zhang/ Dana-Farber Cancer Institute	The Function of RHOA Mutations in the Development of Diffuse Gastric Cancer	RP: This study aims 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 incur higher risks of *H. pylori* infection and radiation exposures, resulting in increased risk of gastric cancer development.	*None to date*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
STOMACH CANCER				
CA160399 $568,800 Open	Choi/ Vanderbilt University Medical Center	Gastric Carcinogenesis in a Novel Genetically Engineered Mouse Model	RP: This study seeks to test the hypothesis that activated K-RAS in metaplastic lineages derived from mature chief cells will lead to the development of gastric adenocarcinoma. MR: Service members are at a higher risk for developing stomach cancer due to increased exposure to *H. pylori.* This study may lead to the development of new therapeutics for stomach cancer.	*Publication: 1*
CA160431 $558,001 Open	El Zaatari/ University of Michigan, Ann Arbor	Targeting B Cell-Mediated Type II Autoimmunity in Gastric Carcinogenesis	RP: *H. pylori* causes gastric metaplasia, which predisposes individuals to develop gastric carcinogenesis (GC). The study aims 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 the development of GC. Military personnel are at a higher risk of acquiring *H. pylori* and therefore at a higher risk for developing GC. This study could provide a better understanding of mechanism underlying how *H. pylori* may lead to GC.	*Publication: 1*
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: This study inteds to test the hypothesis that Gal-3 induces (1) immune suppression by upregulating immune checkpoint protein PDL1 and CD47 in tumor cells, and (2) activation of TAF to secrete inflammatory cytokines (CSF1/CCR2) in the stroma. MR: Japan, Korea, and Taiwan have higher rates of gastric cancer. The major risk factors are *H. pylori*, food pickled with carcinogens, and high salt diets. Troops deployed to these regions are at a higher risk for developing GC. This study aims to improve survival of GC patients among our troops and their families.	*None to date*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
STOMACH CANCER				
CA160445/P1/P2 $1,598,400 Open	Ajani; Hanash; Calin/ The University of Texas MD Anderson Cancer Center	Discover Novel Therapeutic Strategies for Peritoneal Metastases from Gastric Adenocarcinoma	RP: This study aims 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 a higher risk for developing GC. Identification of novel drug targets will benefit Service members with GC.	*None to date*
CA160479 $531,636 Open	Goldenring/ Vanderbilt University Medical Center	Identification of Metaplastic and Pre-Neoplastic Stem/Progenitor Cells	RP: GC 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 a higher risk for developing 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 GC development.	*None to date*
CA160616 $633,483 Open	Lee/ The University of Texas MD Anderson Cancer Center	Marker-Based Targeting of Chemoresistant Subtype of Gastric Cancer Discovered by Proteomics	RP: The study aims to (1) develop and validate biomarkers for subtype A in clinical samples; (2) validate resistance in a PDX model; and (3) determine the molecular mechanisms of chemoresistance in subtype A. MR: GC is considered a service-connected malignancy due to exposures to ionizing radiation and to *H. pylori*. This study intends to develop a biomarker-based treatment strategy for GC patients.	*Publication: 1*
CA160688 $518,400 Open	Wang/ University of California at San Francisco	Cytoskeletal Modulation Results in Drug Resistance of Gastric Cancer Through Inhibition of p53-Mediated Apoptosis	RP: Inhibition of the cytoskeletal RhoA-ROCK-myosin axis results in attenuation of p53, decreased apoptosis, and increased tumor survival. This study aims to test whether MYH9 can be a biomarker for treatment response, and to examine whether re-activated p53 can enhance tumor killing. MR: GC is considered a service-connected malignancy due to exposures to ionizing radiation and to *H. pylori*. This study intends to develop a new biomarker and treatment strategy.	*Publication: 1* *Presentation: 1*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
STOMACH CANCER				
CA160801 $619,375 Open	Korn/ University of California at San Francisco	Rational Therapies for Diffuse-Type Gastric Cancer	RP: This study aims to test the hypothesis that TGF-beta and related pathways may be therapeutic targets in diffuse type GC. MR: Military personnel are at a higher risk for developing GC due to exposures to *H. pylori* infection and radiation. This study will help develop more efficacious treatments for this disease.	*None to date*
CA160928 $239,999 Open	Veeranki/ The University of Texas MD Anderson Cancer Center	Cyclin-Dependent Kinase 9, a Potential Therapeutic Target in Gastric Adenocarcinoma: An *In Vitro* and *In Vivo* Efficacy Study	RP: This study aims to test the hypothesis that CDK9 is a critical mediator of growth and metastatic progression in gastric adenocarcinoma (GAC). Functional downregulation of CDK9 will inhibit local growth and distant metastasis in GAC. MR: Military personnel are at a higher risk for developing GC due to exposures to *H. pylori* infection and radiation. This study will help develop new inhibitors of CDK9 to treat GAC.	*Presentations: 2* *Awards: 3*
CA160948 $262,500 Open	Nagaraja/ Dana-Farber Cancer Institute	Cyclin E1 in Gastric Cancer	RP: This study intends to test the hypothesis that cyclin E1 (CCNE1) activation promotes genomic instability and development of GC. MR: Military personnel are at a higher risk for developing GC. This study will provide a better understanding of the pathogenesis of GC by developing mouse models of this disease.	*None to date*
CA170308 $620,041 Open	Wilson/ Vanderbilt University Medical Center	Novel Intervention for Helicobacter pylori-Induced Stomach Cancer: Chemoprevention by Scavengers of Electrophiles	RP: This study aims to test the idea that electrophiles derived from *H pylori*-induced gastric inflammation causes histone and DNA modification, thus causing genomic instability. MR: Military personnel are at a higher risk for developing GC. This study is expected to lead to improved care for patients with *H. pylori* infection, by reducing the development of GC and associated socio-economic parameters in military and veteran populations.	*None to date*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
STOMACH CANCER				
CA170399 $616,018 Open	Merrell/ Uniformed Services University of the Health Sciences	Helicobacter pylori-Induced DNA Double-Strand Breaks and Gastric Cancer	RP: This study intends to determine whether *H pylori* infection induces R-loops, and whether blocking R-loop formation will decrease DNA damage. MR: Military Service members and veterans have higher exposure to *H Pylori* and are at an increased risk for developing stomach cancer.	*None to date*
CA170906 $640,000 Open	Song/ The University of Texas MD Anderson Cancer Center	Discover Novel Biomarkers/Targets for Advanced Gastric Adenocarcinoma Patients by Exploring Tumor-Associated Exosomes from Malignant Ascites	RP: This study aims to characterize tumor associated exosomes from PC supernatant by proteomic profiling to identify new biomarkers and establish new therapeutic targets for GAC patients. MR: Military personnel are at a higher risk for developing GC. This proposal will lead to novel target therapy and preventative strategies for high-risk GAC metastasis.	*None to date*
CA170928 $574,768 Open	Fingleton/ Vanderbilt University	Advancing the Understanding of Lymphatic Metastasis in Colorectal and Gastric Cancers	RP: This study intends to test the hypothesis that implantation of GC or CRC cells into mesenteric lymphatic vessels is a robust model for lymphatic metastasis of CRC and GC that can be exploited for improving cancer care. MR: Military personnel are at a greater risk for developing lymphoma due to exposure to cytotoxins and chemicals during deployment. This study will improve understanding of lymphatic metastasis.	*None to date*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
STOMACH CANCER				
CA180425 $564,173 Open	Woo/ City of Hope Beckman Research Institute	Discovery of Immune Biomarkers That Predict Response to a Novel Chimeric Immuno-Oncolytic Virus Encoding Anti-PD-L1 in Gastric Cancer Peritoneal Carcinomatosis	RP: This study aims to test the hypothesis that multiple tumor intrinsic and extrinsic factors influence the infectivity and tumoricidal activity of CF33-antiPD-L1, and thus certain cellular and molecular signatures of GCPC will be predictive of viral efficacy. The goals of the study are to (1) identify the cellular and molecular profile of GCPC that correlates with infection, replication, tumor killing, and anti-PD-L1 production after CF33-antiPD-L1 infection; and to (2) design a molecular assay that can inform selection of patients who will respond to CF33-antiPD-L1 therapy. MR: GC disproportionately affects U.S. military Service members, veterans, and their beneficiaries. Military personnel are at a high risk for environmental exposures to *H. pylori* and Epstein-Barr viral infections, ionizing radiation, and for smoking tobacco. Of note, veterans and young, Active Duty Hispanic men (about 15 percent of U.S. military personnel) are diagnosed with advanced GC stages at higher rates than the general American population. Thus, effective, tailored treatment strategies to eliminate GCPC are desperately needed to decrease both military and civilian lives lost to GC.	*New research – no outcomes reported to date*
CA180494 $624,000 Open	Basu/ Ohio State University	Angioprevention of Stomach Cancer	RP: This study will test the hypothesis that targeting angiogenesis in pre-neoplastic gastric lesions might prevent GC. MR: This study may identify an orally active novel antiangiogenic agent (i.e., CA) that can inhibit the initiation and progression of pre-neoplastic gastric lesions to GC among Active Duty Service members, veterans, and their family members who harbor these lesions, diagnosed by upper gastrointestinal endoscopy, biopsy, and histopathology.	*New research – no outcomes reported to date*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
STOMACH CANCER				
CA181103 $352,399 Open	Long; Parma/ University of Texas Health Science Center at San Antonio	Gaps in Gastric Cancer Risk Factor Management: Analysis of Electronic Health Data and Provider/Patient Perspectives	RP: This study aims to understand which factors and their resulting interactions contribute to disparities in the testing and treatment of *H. pylori*- related gastric disorders, as well as GC diagnosis and treatment, among Latinos relative to NHW. MR: GC is a disease that disproportionately affects U.S. military Service members, veterans, and their beneficiaries. Affected Service members are ethnically diverse. Understanding the underlying mechanism for the disparity of *H. pylori* infection and related gastric disorders will benefit underserved Service members.	*New research – no outcomes reported to date*

REFERENCES

1. Crawford RS, Wu J, Park D, and Barbour GL. A study of cancer in the military beneficiary population. *Mil Med* 2007;172:1084-1088.

2. Lee T, Williams VF, Taubman SB, and Clark LL. Incident diagnoses of cancer in the active component and cancer-related deaths in the active and reserve components, U.S. Armed Forces. 2005-2014. *MSMR* 2016;23:23-31.

3. Carter AJR and Nguyen CN. A comparison of cancer burden and research spending reveals discrepancies in the distribution of research funding. *BMC Public Health* 2012;12:526.

APPENDIX A: FY 2013–FY 2015 RESEARCH PROGRESS AND MILITARY RELEVANCE OF CLOSED AWARDS

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
BLOOD CANCER				
CA130124 $362,154 Closed	Magee/ Washington University	Temporal Changes in FLT3-ITD Regulation of Stem Cell Self-Renewal and Leukemogenesis	RP: This study aimed to test whether a receptor tyrosine kinase FLT3-ITD depletes hematopoietic stem cells; whether fetal and adult hematopoietic progenitors have different FLT3-ITD-driven signal transduction mechanisms and gene expression; and whether ectopic Lin28b expression impedes FLT3-ITD-driven depletion and leukemogenesis. MR: Service members are at a greater risk of exposure to mutagens than are civilians; therefore, it is important to understand how the developmental history of a given leukemia will influence its genetic makeup and response to therapy.	*Publications: 2* *Presentations: 3* *Funding Obtained: 1*
CA130155 $482,404 Closed	Atchison/ University of Pennsylvania	YY1 Control of AID-Dependent Lymphomagenesis	RP: This study focused on examining the role of the transcription factor YY1 in B-cell lymphomagenesis or disease progress. MR: Vietnam War veterans are at a greatly increased risk for developing Hodgkin's lymphoma, Non-Hodgkin's lymphoma, and chronic lymphocytic leukemia. Many of these cancers initiate due to activation-induced cytidine deaminase activity. Additionally, children of Vietnam War veterans are at an increased risk for developing acute myeloid leukemia.	*Publications: 2*
CA130247 $534,407 Pending Closeout	Wang/ University of North Carolina at Chapel Hill	Epigenetic Therapy of Hematopoietic Malignancies: Novel Approaches for Tissue-Specific and Global Inhibition of EZH2 Enzymatic Activities	RP: This study aimed to develop novel means to target two novel proteins of B-cell derived tumors for anticancer therapies, and to investigate the mechanism by which these proteins induce B-cell related tumors. MR: Blood cancers, including lymphoma and multiple myeloma, are associated with exposure to chemical and biological agents from the Vietnam and Gulf Wars.	*Publications: 9* *Funding Obtained: 1*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
BLOOD CANCER				
CA130256 $364,538 Pending Closeout	Lapalombella/ Ohio State University	Understanding and Targeting the Nuclear Export Protein XPO1 in B-Cell Malignancies	RP: This study aimed to determine the effects of the XPO1 mutations on the development and pathogenesis of chronic lymphocytic leukemia (CLL). MR: CLL is more prevalent among veterans, particularly in those who served during the Vietnam War, due to the exposure to AO and other toxins.	*Publications: 2* *Presentations: 3* *Degree/Employment:* *1 - Assistant Professor* *Funding Obtained: 5*
CA130371 $265,658 Pending Closeout	Cardelli/ Louisiana State University Health Sciences Center	Exploring Potential Link Between Bacterial Flora, Myeloid-Derived Suppressor Cells (MDSC), and Extraintestinal Tumor Development	RP: This study aimed to test whether germ-free mice will show reduced tumor growth and enhanced antitumor immune response. MR: Military members and their families incur exposures 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 among military personnel more profoundly than the public.	*None to date*
CA130445 $465,000 Closed	Jamieson/ University of California San Diego	Identification of Novel RNA Editing Biomarkers of Human Leukemia Stem Cell Generation	RP: This purpose of this study was to test the hypothesis that activation of foreign nucleic acid sensing and editing pathways, such as ADAR1, during acute myeloid and lymphoid leukemia propagation results from retention of viral genetic material in dormant stem cells. MR: This research will broaden our understanding of risk factors for blood cancer progression and therapeutic resistance in military personnel. New therapeutic strategies could be designed to protect against carcinogenic infectious agents in the military environment.	*Publications: 4* *Presentations: 33* *Patents: 1 provisional patent application, 1 PCT patent application* *Funding Obtained: 5*

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

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
COLORECTAL CANCER (CRC)				
CA150731 $130,751 Pending Closeout	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: This study assessed the role of p53 mutations in the alteration of metabolism and therapeutic sensitivity of 5-Fluorouracil (5-FU), the major component of CRC chemotherapy. Results support the idea that different p53 mutations contribute to 5-FU resistance in unique ways, and that DPYD expression can either support resistance or sensitivity to 5-FU depending on the specific p53 mutation. *In vivo* studies demonstrate that loss of p53 in cells results in tumor cell resistance to 5-FU. These studies provide rationale that CRC patients should be tested for DPYD and p53 status before beginning 5-FU therapy. MR: CRC is the third most frequently occurring cancer in the military population, occurring up to eight percent among veterans and five percent among Active Duty personnel.	*Presentation: 1* *Publication: 1* *Employment:* *1 - Post-Doctoral Position* *Degree Obtained: PhD* *Miscellaneous: 2*
CA150808 $125,250 Pending Closeout	Tosti/ Albert Einstein College of Medicine	The Role of Mismatch Repair and Microbiome in Inflammation-Associated Colon Cancer	RP: This study investigated the relationship between TGFBRII inactivation and the colonic microbiota in DNA mismatch repair (MMR)-driven tumorigenesis. This study investigated the differences in survival, tumor incidence/location, and histopathology of MMR-impaired mice, and demonstrated that these tumors more closely mimic the disease phenotypes observed in human patients. Additionally, Msh2/TgfBRIIhu double mutant mice have reduced colon cancer survival. The PI plans to further examine the impact of microbiota alteration on tumorigenesis within these mice. MR: CRC represents the third most common cancer type worldwide. Genetic instability is a major cause in CRC initiation and progression, and DNA MMR is essential to preserve genome integrity and suppress tumorigenesis.	*None to date*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
COLORECTAL CANCER (CRC)				
CA150866 $91,144 Pending Closeout	Tackmann/ University of North Carolina-Chapel Hill	Characterizing the Role of Hep27 in Liver and Colorectal Cancer Stress Tolerance	RP: This study aimed to characterize the role of Hep27 overexpression in colon cancer. The investigator hypothesized that Hep27 increases reactive oxygen species (ROS) tolerance, which contributes to therapeutic resistance. Using liver and CRC cell lines, this research suggested that Hep27 does not play a role in tolerance to oxidative stress. The PI successfully defended her PhD thesis and obtained new employment. MR: The military population is particularly vulnerable to HCC, given the higher rates of behavioral and environmental exposures that are risk factors of this disease, including HCV infection, obesity, diabetes, and alcohol abuse.	*Degree Obtained: PhD, UNC* *Employment Obtained: Clinical Research Scientist*
CA150873 $127,125 Pending Closeout	Sauer/ New York University School of Medicine	Structure and Function of the Reduced Folate Carrier	RP: This project intended to solve the 3D crystal structure of the human Reduced Folate Carrier (hRFC) protein. Folates play an important role in cell metabolism. Limitations in cellular folate levels or defects in the folate cycle have been linked to cancer. Unfortunately, the 3D structure was not resolved due to technical issues, but the PI obtained follow-on funding to perform the structural analysis of the proteins designed in this project using a new technique. MR: A structural description of hRFC is necessary for structure-based drug design of novel chemotherapeutics acting on the folate pathway. This work will directly benefit Service members, their families, and beneficiaries by accelerating the development of new chemotherapies.	*Funding Obtained: 1* *Publications: 2*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
COLORECTAL CANCER (CRC)				
CA150899 $113,479 Pending Closeout	Carpenter/ St. Louis University	Colorectal Cancer Immunotherapy by Pharmacological Suppression of Liver X Receptor Activity	RP: This study aimed to investigate the role of liver X receptor (LXR) activation in the process of immune evasion by tumor cells. The study will determine whether blocking the receptor/ligand interaction of activating signals released by tumors is sufficient to stimulate T-cell response to CRC cells *in vitro*. *In vivo* experiments using an LXR blocking agent show CRC tumor growth inhibition. This anti-tumor effect requires an intact immune system suggesting that this compound is not acting directly on the tumor but instead boosting the immune recognition and clearance of these cells. MR: There are approximately one million new cases of CRC worldwide per year. It is the third most diagnosed cancer within the VA system. The identification of novel treatments for CRC is therefore relevant to the health and well-being of military personnel and their beneficiaries.	*Presentations: 2*
GENETIC CANCER				
CA140321 $528,000 Pending Closeout	MacPherson/ Fred Hutchinson Cancer Research Center	Developing a KMT2D/MLL2-Deleted Preclinical Mouse Model of Bladder Urothelial Cancer	RP: This study's objectives were to develop a mouse model of bladder cancer that exhibits several bladder cancer markers, and test a new hypothesis for treating bladder cancer. The 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 among Active Duty military than the general population, and is particularly high among deployed military. This work has potential to improve survival rates in military personnel and their families who develop bladder cancer.	*None to date*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
GENETIC CANCER				
CA150795 $128,550 Pending Closeout	Ghisays/ Memorial Sloan Kettering Cancer Center	RTEL1 and Genome Stability	RP: In this study, the PI found that a mutation of RTEL1 commonly found in patients prevents RTEL1 from self-associating, which negatively affects its functionality. 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 myeloid proliferative disorders and cancer development will provide unique insights that can be immediately translated into clinical care.	*Funding Obtained: 1* *Presentation: 1*
CA150794 $127,125 Pending Closeout	Daniloski/ New York University School of Medicine	Elucidate the Mechanism of Telomere Maintenance in STAG2 Mutated Tumor Cells	RP: The purpose of this study was to test the hypothesis that STAG2 mutated tumors utilize both telomerase and ALT to elongate their telomeres, and that forced resolution of the persistent telomere cohesion will lead to rapid cancer cell death. MR: Due to exposure to ionizing radiation, chemicals, and environmental carcinogens, military personnel are at particularly high risk for DNA damage that can lead to increased gene mutations and promote cancer formation. This study addresses how tumors carrying mutations in STAG2 gene maintain their telomeres.	*Presentations: 2* *Publication: 1*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
GENETIC CANCER				
CA150827 $108,350 Pending Closeout	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. In this study, the PI proposed designing and synthesizing Cobalt (III) Schiff Bases that target mutant p53 and prevent aggregation. At the end of the award, the PI was nearly complete with the Cobalt (III) Schiff Bases synthesis. MR: Mutations in p53 are the most common clinically observed cancer-causing mutations, present in over 50 percent of all cancers. Development of a novel therapeutic would benefit Service members, veterans, and military beneficiaries who are affected by cancers containing p53 mutations.	*Miscellaneous: 2*
CA150844 $80,370 Pending Closeout	Wadugu/ Washington University	The Role of Mutant U2Af1 in the Pathogenesis of Myelodysplastic Syndromes	RP: The PI created a novel mouse model of myelodysplastic syndrome (MDS) to if the two mutations that often co-occur in the same tumor, U2AF1 and ASXL1, lead to tumorigenesis. Results of the project show that up to 12 months post-induction of the mutations there is no cooperation between U2AF1 and Asxl1 mutations to induce hematopoietic abnormalities or development of MDS/AML, regardless of the order of mutation acquisition. MR: Identifying genetic mutations contributing to MDS initiation is key to developing effective prognostic and therapeutic strategies. The mouse models used here will be valuable reagents for the research community to test drugs in future preclinical studies.	*Presentations: 2* *Miscellaneous: 2*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
GENETIC CANCER				
CA150882 $125,694 Pending Closeout	Hsieh/ Cornell University Weill Medical College	Characterization of Ran Binding Protein (RANBP6) as Candidate Tumor Suppressor	RP: This study focused on testing the hypothesis that the tumor suppressor function of ran binding protein 6 (RanBP6) stems from its role as regulator of nuclear import/export. The PI will identify RanBP6 substrates, characterize RanBP6 mutations that are common in multiple types of cancer, and explore the tumor suppressor activity of RanBP6 in a murine pancreatic organoid model. MR: These studies aim to broaden the currently rudimentary knowledge on how Ran and Ran-binding proteins contribute to tumorigenesis and will provide new opportunities to therapeutically target deregulated growth factor signaling in cancer, which will not only benefit the military families but also the Service members and veterans, who have an increased risk of developing cancer due to a higher chance of exposure to carcinogens.	*None to date*
KIDNEY CANCER				
CA13002 $474,562 Pending Closeout	Czyzyk-Krzeska/ University of Cincinnati	Effects of Tobacco Smoke (TS) on Growth of Clear Cell Renal Cell Carcinoma (ccRCC)	RP: This study aimed to identify somatic mutations in DNA extracted from clear cell renal cell carcinoma (ccRCC) tumors from male veterans and heavy smokers, compared to matched ccRCC patient non-smokers, and to 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 in non-smokers. MR: There is a high prevalence of smoking among male Active Duty military personnel and veterans, as well as a higher rate of kidney cancer, compared to the non-military population.	*Funding Applied for: 1*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
KIDNEY CANCER				
CA130458 $602,996 Pending Closeout	Ebos/ Health Research Inc., Roswell Park Division	Distinguishing Tumor- and Stromal-Mediated Mechanisms of Resistance and Rebound in Models of Metastatic Renal Cell Carcinoma	RP: This study aimed to 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 are at a higher risk for developing kidney cancer due to deployment-related exposures to environmental hazards.	*Publications: 6* *Presentations: 7* *Miscellaneous: 3*
CA140443 $340,501 Pending Closeout	Zhang/ University of North Carolina at Chapel Hill	Validation of ZHX2 as a Novel pVHL E3 Ligase Substrate and Its Role in Kidney Cancer	RP: This study intended to confirm that zinc finger homeobox protein 2 (ZHX2) levels are negatively regulated by the tumor suppressor pVHL, and to 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 percent of Active Duty personnel do, is a significant risk factor for RCC; and (2) occupational exposure to heavy metals, paints, organic solvents, and other combat-related chemicals significantly increases the risk of RCC.	*Presentations: 3* *Funding Obtained: 1* *Publication: 1*
CA150289 $779,349 Pending Closeout	Rastinejad/ Sanford-Burnham Medical Research Institute, Orlando	Novel Hypoxia-Directed Cancer Therapeutics	RP: In this study, the PI studied the mechanism of action of three HIF-binding antagonists, and found that each antagonist displaced residue M252 from the interior of ligand binding pocket to the exterior heterodimerization interface. The extent that the antagonist displaced M252 correlated with the potency of the antagonist. Each antagonist functioned by destabilizing the protein-protein interaction between HIF and its binding partner. MR: HIF-targeted drugs can broadly impact both civilian and military personnel suffering from advanced cancers. The new treatment options that may ultimately emerge from this research would benefit patients with a variety of cancers that are currently resistant to existing treatments.	*Publications: 3* *Presentations: 2* *Employment:* *1 - Professor*

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

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
MELANOMA/SKIN CANCER				
CA130184 $585,000 Closed	Ronai/ Sanford-Burnham Medical Research Institute	Siah1/2 Ubiquitin Ligases in ER Stress Signaling in Melanoma	RP: This study aimed to determine the significance of the Siah2-hypoxia-ER stress regulatory axis in melanoma development and progression, and to evaluate the use of Siah1/2 and ER stress inhibitors as potential therapeutics. Results confirmed that Siah2 presence on tumors inhibits immune cell infiltration through an immune checkpoint mechanism, and loss of siah2 expression in melanoma cells could slow down tumor development *in vivo*. This study resulted in the development of a first-in-class inhibitor for ubiquitin ligases that inhibits "cancer-like" phenotypes within cultured cells. MR: Risk for melanoma development is significantly higher among a younger age group (i.e., 16-25 years of age), making development of new treatments and prevention of melanoma pertinent for Active Duty Service members.	*Publications: 3* *Presentations: 9* *Patent: 1*
CA130351 $550,800 Pending Closeout	Wang/ Medical College of Wisconsin	Novel Combinatorial Immunotherapy for Melanoma	RP: This study aimed to enhance understanding of the role of V-domain Immunoglobulin Suppressor of T cell Activation (VISTA) in establishing the immunosuppressive tumor microenvironment. In this project, the PI mapped the molecular pathway of activity through which VISTA controls the inflammatory response, and identified the populations of immune cells regulated by VISTA. Inhibition of VISTA signaling looks to synergize with T cell signaling *in vivo* to activate immune cells within the normally suppressive tumor microenvironment. MR: Melanoma is recognized as one of the rising cancers among military personnel, especially field agents exposed to harsh environmental elements, such as sun exposure.	*Presentation: 1* *Publication: 1*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
MELANOMA/SKIN CANCER				
CA130409 $464,034 Closed	Abdel-Malek/ University of Cincinnati	Differential Impact of P16 Mutations With or Without Coexpression of MC1R Mutation on the UV Response of Melanocytes, and Hence on the Risk for Melanoma	RP: This study aimed to determine the mechanisms by which co-expression of mutations in p16 and loss-of-function allelic variants of MC1R synergistically increase the risk for melanoma. It tested the impact of three mutations in p16 that are present in familial melanoma cases on melanocyte transformation, in the absence or presence of non-functional MC1R. Findings indicate that heterozygosity for p16 mutations is not enough to affect UV exposure sensitivity within these cells. Results suggest that although p16 mutations are sufficient to cause melanoma in patients, the transformation to cancer does not seem to be due to abnormal melanocyte function. MR: Understanding the tissue biomarkers that predispose populations to melanoma will be of considerable importance for Service members stationed in environments with high UV exposure.	*Presentation: 1* *Funding Obtained: 2* *(both R21s from the NCI)*
CA140020 $489,199 Pending Closeout	Cui/ Boston University Medical Campus	Dot1L is a Lineage-Specific Tumor Suppressor in Melanocyte	RP: This project determined the role of Dot1L in UV-induced DNA damage and repair and melanoma development. Using melanoma cell lines and *in vivo* animal models, the investigator showed that DOT1L functions as a tumor suppressor. Loss of DOT1L in combination with BRAF mutations make melanocytes more sensitive to melanoma development. MR: Individuals that serve in tropical areas and receive heavy sun exposure during their early adulthood may be at a higher risk for developing melanoma later in life.	*Publication: 1*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
MELANOMA/SKIN CANCER				
CA140189 $554,400 Pending Closeout	Fourcade/ University of Pittsburgh	Role of the Inhibitory Receptor TIGIT in the Regulation of CD4+ Tregs in Patients with Advanced Melanoma	RP: This project assessed the role of the inhibitory receptor TIGIT on suppressing the melanoma antitumor response. Results showed that TIGIT is expressed on Tregs in the tumor and in peripheral immune cells; TIGIT-positive cells create a suppressive environment so that other immune cells cannot activate to target the tumor. TIGIT competes with CD226 for the same ligand PVR, so reversing the suppressive functions of the Tregs requires both activation of CD226 and blockage of TIGIT, which enhances anti-tumor T cell function in the tumor. Finally, the TIGIT-positive Tregs can be depleted with anti-TIGIT antibodies, which recruit Natural Killer cells to attack the Tregs. These findings strongly support the development of novel immunotherapies using anti-TIGIT antibodies in combination with activating CD226 in melanoma patients to decrease the suppressive Tregs in the tumor microenvironment. 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 with intense sun exposure, improved therapies will provide higher quality of life for military members and their families.	*Presentations: 4* *Publication: 1*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
MELANOMA/SKIN CANCER				
CA140216 $460,477 Pending Closeout	Harbour/ University of Miami Coral Gables	Development of Targeted Molecular Therapy for Cancers Harboring BAP1 Mutations	RP: This project developed a novel high-throughput screening assay to identify compounds for treating cancers with BAP1 mutations, such as uveal melanoma and mesothelioma. The investigator identified one compound, quisinostat, which rescues the BAP1-deficient phenotype. In BAP1-deficient uveal melanoma mouse models, quisinostat results in anti-proliferative and anti-tumorigenic properties. These results will inform the development of clinical trials for patients with BAP1-mutant cancers. MR: BAP1 is frequently mutated in the most lethal and treatment-resistant cancers such as melanoma, mesothelioma, and kidney cancer. The development of a BAP1 signaling-specific therapeutic is of significant importance to military personnel who are at higher risk of these cancers due to environmental exposures while deployed.	*Presentation: 1*
CA140238 $547,200 Pending Closeout	Su/ University of North Carolina at Chapel Hill	Central Tolerance Blockade to Augment Checkpoint Immunotherapy in Melanoma	RP: The goal of this project was to develop an antibody that would enhance the effect of immunological checkpoint inhibitors when used in combination against melanoma growth in mice. Overall, this project demonstrated that in mouse models of melanoma, anti-RANKL (denosumab), has a synergistic effect with checkpoint inhibitors anti-CTLA4 and anti-PD1 in decreasing tumor growth and prolonging survival. Results of this project informed the development of a Phase II clinical trial in melanoma patients using anti-RANKL in combination with checkpoint inhibitors. 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.	*Publications: 2* *Presentation: 1* *Clinical Trial: 1 (Phase II)*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
MELANOMA/SKIN CANCER				
CA140389 $391,766 Pending Closeout	Siegel/ McGill University	Development of Rational Combination Therapy Strategies for the Treatment of Metastatic Melanoma	RP: The aim of this project was to determine whether an antibody-drug conjugate can be employed in combination with BRAF kinase inhibitor therapy to overcome 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. The investigator also identified three distinct classes of BRAF mutations that respond differently to targeted therapies and have important implications for future drug development. 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: 4* *Presentations: 6* *Clinical Trials: 2*
CA130414 $508,500 Closed	Bernstein/ Mount Sinai School of Medicine	Identifying Epigenetic Modulators of Resistance to ERK Signaling Inhibitors	RP: This study aimed to decipher the epigenetic mechanisms underlying melanoma drug resistance, by mapping the epigenomic landscape of melanoma cells that have acquired resistance to signaling inhibitors. Research revealed novel and critical epigenetic regulators of resistance to RAF inhibitors and RAF inhibitors + MEK inhibitors. Loss of function screening also identified new drivers of RAFi resistance in melanoma cells. MR: Cutaneous malignant melanoma is the most lethal form of skin cancer. It arises from the pigment-producing cells known as melanocytes, and results primarily from sun exposure – an environmental influence associated with military exposures.	*None to date*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
MELANOMA/SKIN CANCER				
CA140485 $474,000 Pending Closeout	Andarawewa/ University of Virginia	The Therapeutic Effects of Ultrasound-Mediated Immune Responses in Melanoma	RP: The goal of this project was 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. After optimizing the parameters of this method, the investigator demonstrated that FUS increases the numbers of immune cells within the tumor, which play a role in killing tumor cells. Furthermore, this method is synergistic with immune checkpoint inhibitors. Results of this study informed the approval of a clinical trial. MR: Melanoma incidence is higher in the U.S. military population than the U.S. population as a whole. Improvement to the current standard of care would therefore affect military families preferentially.	*Publication: 1* *Presentations: 5* *Funding Obtained: 1 grant* *Clinical Trial Funded: 1*
CA130537 $368,031 Pending Closeout	Khanna/ University of Connecticut Health Center, Farmington	Development of Cytomegalovirus-Based Vaccines against Melanoma	RP: This project developed and tested the efficacy of cytomegalovirus (CMV)-based anti-melanoma vaccines expressing single or multiple tumor antigens. *In vivo* experiments showed that tumor antigen expressing CMV can generate potent, long-lasting antitumor immunity due to recruitment of CD8+ and CD4+ T cells. This CMV-based vaccine was able to protect mice from a highly metastatic form of melanoma, reducing tumor number and significantly slowing tumor growth in these mice. MR: Deployment to areas of high UV exposure 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 affected personnel.	*Publications: 2* *Presentations: 3* *Employment: Associate Professor, New York University*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
MELANOMA/SKIN CANCER				
CA140666 $447,000 Pending Closeout	Xie/ University of Georgia	Treating Melanoma Metastases with a Novel Photodynamic Approach	RP: This project evaluated the efficacy of a new target therapy to treat metastatic melanoma, using X-ray inducible photodynamic therapy (X-PDT). In this system, photosensitive nanoparticles are conjugated to compounds that home to tumors. External X-rays are then applied to activate the photosensitive nanoparticles. In a mouse model of melanoma with lung metastasis, X-PDT resulted in significant tumor suppression compared to X-ray treatment alone. Furthermore, the X-PDT prevented metastasis to other organs. This project could lead to the expansion of PDT applications for cancer treatment. MR: The incidence rate of melanoma is roughly 62 percent greater among Active Duty military than in the general population. A new treatment for this disease would greatly benefit military personnel and their families.	*Publications: 10* *Presentations: 5*
CA140744 $489,165 Pending Closeout	Fisher/ Massachusetts General Hospital	Stem Cell-Loaded Oncolytic Viruses for Metastatic Melanomas	RP: This study was conducted to evaluate the therapeutic potential of a virus-mediated tumor-selective therapy *in vitro* and in a mouse model of melanoma brain metastasis. The PI demonstrated that virus alone is inefficient at killing melanoma brain metastasis using a mouse model. However, when MSC are infected with the virus and used as a vehicle for transporting these particles to the tumor site, oncogenic cell clearance is greatly increased. When mice are treated with virus-loaded MSCs in combination with anti-PD1 therapy, tumor growth and mouse survival are greatly affected, and long-term survival was observed in a subset of treated mice. MR: Melanoma is of particular interest to the military, given that Active Duty personnel are often required to be outside for prolonged periods of time while stationed in sun-intense locals. Thus, military men and women face the potential for long-term risk of melanoma.	*Publication: 1* *Funding Obtained: 1* *Websites: 3*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
MELANOMA/SKIN CANCER				
CA150197 $657,255 Pending Closeout	Zheng/ Massachusetts General Hospital	Role of the Lipid Phosphatase INPP48 in the Development of Resistance to BRAF Pathway Inhibition	RP: This project aimed to 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. The PI confirmed that reduced INPP4B expression causes resistance to BRAF inhibitors in melanoma cell lines. These results suggest that INPP4B expression could be a predictive biomarker of BRAF inhibitor efficacy in melanoma patients. MR: Military Service members who work in sun-intense areas are at great risk for developing melanoma. In fact, it has been demonstrated that the incidence of melanoma is higher among the military population than the general population.	*None to date*
CA150340 $665,999 Pending Closeout	Yan/ Yale University	Dissecting the Roles of ARID2 Tumor Suppressor in Metastatic Melanoma	RP: The goals of this project were to determine how putative tumor suppressor ARID2, an epigenetic regulator, controls melanocyte reprogramming, and to investigate whether targeting another epigenetic regulator, RBP2, can be used to treat patients with ARID2 loss. The investigator performed *in vitro* and *in vivo* studies to examine the impact of ARID2 gain-of-function and loss-of-function. Sequencing studies revealed potential novel roles for this gene, including in immune functions. MR: As the risk for melanoma development 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.	*Presentations: 4* *Publications: 2*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
MELANOMA/SKIN CANCER				
CA150391 $605,018 Pending Closeout	Wang/ University of North Carolina at Chapel Hill	Tissue-Engineered Cancer Metastasis to Improve the Abscopal Effect and Cancer Immunotherapy in Melanoma	RP: This project investigated the utility of using irradiated melanoma lung metastasis (mets) as an immunizing agent to stimulate an anti-cancer response in tumor bearing mice. Using mouse melanoma cells, the PI was able to engineer lung metastases *in vitro*. These mets were then further processed to create a cancer vaccine. In mouse models of melanoma, this vaccine reduces tumor growth, improves survival, and prevents lung metastasis when used in combination with checkpoint inhibitor immunotherapy. These results will inform the next stage of the investigator's research, which is to use melanoma CTC to create a similar vaccine for human use. MR: Improvements in the management of metastatic melanoma can be particularly beneficial to military populations. Melanoma is more common among members of the military than 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 serving as Active Duty members of the Armed Services.	*Publication: 1*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
MELANOMA/SKIN CANCER				
CA150492 $632,000 Pending Closeout	Zaidi/ Temple University	UV-Induced Epigenetic Field Effect as a Target for Melanoma Therapy and Prevention	RP: The goals of this project were to investigate the role of UV irradiation-induced epigenetic changes in melanoma initiation, and to determine the utility of these changes as biomarkers. The PI demonstrated that UV-irradiated mouse and human cells show significant changes in DNA methylation patterns, compared to non-irradiated cells. Findings from this study contribute to the overall understanding of how DNA is impacted by excessive sun exposure. Additionally, the identification of genetic biomarkers could be used to assess an individual's risk for skin cancer development. MR: UV solar radiation is the most ubiquitous environmental carcinogen. 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 are vital to devising preventive and therapeutic strategies for military personnel and the general public.	*Presentations: 2*
CA150776 $131,250 Pending Closeout	Badrinath/ Dana-Farber Cancer Institute	Development of Epitope-Focused Tumor Vaccine to Prevent Escape from Immune Surveillance by the NKG2D Pathway	RP: This study optimized a MICA alpha3-based vaccine and validated its anti-tumor effect against subcutaneous melanomas and metastasis in mice. Tumor growth slowed and survival greatly increased among immunized mice challenged with MICA expressing tumors. MR: Active Duty Service members are often exposed for prolonged periods to UV radiation, which is the major risk factor in the development of malignant melanoma.	*None to date*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
MELANOMA/SKIN CANCER				
CA150796 $124,874 Pending Closeout	Zhang/ Yale University	Epigenetic Regulation of Histone Demethylase JARID1B in Melanoma	RP: This study investigated the mechanism by which JARID1B regulates melanoma stem cells, and provided evidence for whether JARID1B targeting should be based on its activity, or on its interactions with key transcription factors or co-activators. Findings from this study support the hypothesis that JARID1B acts through PGC-1α, a metabolic master regulator, to alter melanoma growth parameters. MR: Military Service members and veterans face a higher risk for developing melanoma and other skin cancers.	*Presentation: 1*
CA150804 $127,125 Pending Closeout	Ribeiro; Muniz/ Icahn School of Medicine at Mount Sinai	Endogenous Alarmins in the Progression of Melanoma	RP: The project investigated MMP-2 signaling, the mechanisms by which MMP-2 promotes melanoma progression. The PI identified that MMP-2 directly interacts with TLR2 and TLR4, which are both required for MMP-2 induced signaling. Both tumor incidence and tumor growth were reduced in mice with immune cells lacking TLR2 and TLR4, when compared with WT recipients, suggesting that loss or inhibition of these receptors could be protective against melanoma development. These results indicate the MMP-2 signaling complex could be a potential target for inhibiting tumor growth and progression. MR: Reports indicate that melanoma rates are higher among Active Duty military personnel compared to the general population, and that exposure to sunlight and UV rays can induce skin cancer later on in life.	*Presentations: 3*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
MELANOMA/SKIN CANCER				
CA150818 $115,500 Pending Closeout	Hong/ University of California Los Angeles	Melanoma Drug Addiction and Its Therapeutic Implications	RP: This study sought 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 its incidence rapidly rising due to constant exposure to sunlight and inadequate protection.	*Publication: 1* *Funding Obtained: 1* *Miscellaneous: 1*
CA150852 $80,934 Pending Closeout	Barkauskas/ Queensland Institute of Medical Research	The Role of Adenosine A2BR in Metastatic Melanoma	RP: This project aimed to determine whether adenosine 2B receptor (A2BR) played a critical role in melanoma metastasis by studying A2BR expression on the tumor cell surface and/or endothelium. No effect on tumor growth or metastasis was observed when A2BR was knocked out within the endothelium of melanoma-bearing mice. MR: Studies have found that 77 percent of military personnel report being exposed to bright sunlight for more than four hours a day while working. This potentially exposes these personnel to high doses of intermittent UV light, shown by preclinical models to drive melanoma metastasis.	*None to date*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
MELANOMA/SKIN CANCER				
CA150863 $100,757 Pending Closeout	Chang/ Memorial Sloan Kettering Cancer Center	A Therapeutic TCR Mimic Monoclonal Antibody for Intracellular PRAME Protein in Melanomas	RP: This project investigated the cellular mechanism by which the cancer specific peptide, PRAME (300-309), is presented on the surface of melanoma cells. The PI found that the immunoproteasome (IP) is more efficient than the constitutive proteasome (CP) at processing PRAME (300-309), and specifically, that the Beta5i subunit seems to be critical for PRAME (300-309) presentation. Additionally, an antibody which recognizes PRAME (300-309) was characterized and shown to bind to the surface of melanoma cell lines. Unfortunately, this antibody did not show efficient binding within solid tumors, which greatly affects its utility as a potential melanoma therapeutic. However, the antibody was therapeutically active against non-solid tumors such as ALL and AML *in vivo*. MR: Since the incidence of melanoma is higher among Active Duty Service members, the knowledge gained from these studies will help design future immunotherapies for military personnel.	*Publication: 1* *Presentation: 1*
CA150887 $112,525 Pending Closeout	Daenthanasanmak/ Medical University of South Carolina	Tumor-Specific Th1/Th17 Hybrid Immunotherapy Against Established Melanoma	RP: This study characterized a novel cell type, hybrid Th1+/Th17+ T cells. Hybrid cells demonstrate superior function in tumor eradication, compared to Th1 or Th17 cells. Hybrid cells persist long-term and develop a memory phenotype that could mount tumor-specific immune responses upon second encounter. These cells also switch to produce interferon gamma as a mechanism to control tumors. These cells are long-lived and possess a stem cell-like phenotype. MR: Melanoma is one of the deadliest forms of skin cancer, particularly in the late stages when the malignant cells have metastasized into other vital organs, such as lung, brain, and abdominal organs. Melanoma affects the general population and military personnel alike.	*Publication: 1*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
MELANOMA/SKIN CANCER				
CA150892 $146,520 Pending Closeout	Li/ Sanford Burnham Prebys Medical Discovery Institute, La Jolla	Control of Immune Checkpoints by the Ubiquitin Ligase RNF5: Implications for Melanoma	RP: This study defined ubiquitin ligase RNF5 as a novel immune checkpoint in melanoma. Inhibiting RNF5 in mice attenuates melanoma cell growth and enhances tumor infiltration of T cells. This was the first study to identify an ubiquitin ligase as an immune check point, which enhances our understanding of how immune cells can be activated to target tumors. MR: Melanoma often develops following prolonged sun exposure. Accordingly, exposure of our Service members to sun during deployment puts young men and women at risk for developing melanoma. For those potentially affected, the disease would likely manifest itself after they leave military service, and would impact not only their health, but also the emotional and financial well-being of their families.	*Presentation: 1* *Publications: 2 in revision*
CA150903 $117,855 Pending Closeout	Wilson/ University of Virginia	Ligand Expression on Tumor-Associated Vasculature Orchestrates CD8+ T-Cell Infiltration into Tumors	RP: This study was conducted 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. The PI found that HR ligands and TIL numbers are modified upon anti-CTLA4 therapy, and the anti-tumor response to therapy correlates with increased HR ligand expression and TIL presence. These changes are dependent upon IFN-gamma signaling. MR: Melanoma commonly occurs among young adults. Many Active Duty Service members are young adults who are frequently overexposed to harmful UV sunlight. This puts them at a high risk for developing melanoma and/or other skin-associated cancers.	*Presentation: 1*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
MESOTHELIOMA				
CA130197 $379,039 Pending Closeout	Shukla/ University of Vermont	Exosomes in Development and Therapy of Malignant Mesothelioma	RP: This project aimed to study the role of exosomes, small lipid bound signaling packages, in the development and therapy of malignant mesothelioma to determine whether exosomes secreted from asbestos-exposed human lung macrophages and epithelial cells can transform human mesothelial cells. Initial research indicates that exosomes generated from epithelial cells and macrophages exposed to asbestos contain a unique proteomic signature, which may be responsible for their uptake by mesothelial cells. Application of these exosomes to mesothelial cells results in gene expression changes within the mesothelial cells. MR: Military and veteran populations are at a higher risk for 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 among veteran and military populations for decades to come.	*Publications: 3* *Presentations: 2*
CA130248 $508,593 Closed	Poznansky/ Massachusetts General Hospital	Development of a Novel Immunotherapy for Malignant Mesothelioma that Combines CXCL12/CXCR4 Blockade with a Mesothelin-Targeted Fusion Protein	RP: This study aimed to develop a novel immunotherapy approach for MM that combines CXCR4 blockade with a mesothelioma-targeted immunogenic fusion protein. The study entailed development of two new mouse models of MM that allow non-invasive monitoring of tumor growth and progression. The PI tested the combination therapy *in vivo* using the two mouse models, and showed that this treatment not only synergizes the antitumor immune effect, but also prolongs mouse survival. MR: Mesothelioma, a cancer induced by respiratory exposure to asbestos, disproportionately affects military personnel. While veterans represent eight percent of the Nation's population, they comprise an astonishing 30 percent of all known mesothelioma deaths in the United States.	*Patents: 2* *Presentations: 2* *Publication: 1*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
MESOTHELIOMA				
CA140269 $388,770 Pending Closeout	Najmunnisa/ University of Florida	Epha2-/-NK Cell Therapy Against Malignant Pleural Mesothelioma	RP: This study aimed to characterize the mechanism of tumor growth inhibition by natural killer (NK) cells lacking the EphA2 gene, using a model of malignant pleural mesothelioma (MPM). The investigator has engineered NK cells lacking EphA2 that can directly target MPM cells *in vivo*. The engineered NK cells are better at upregulating chemicals that induce cell death in MPM cells. This work demonstrates that NK cells can be utilized for immunotherapy in the treatment of mesothelioma. MR: Thirty percent of new cases of malignant pleural mesothelioma are reported in veterans each year. Due to environment exposures including asbestos, veterans are at a high risk for developing this fatal disease.	*Presentations: 2* *Publication: 1*
CA150787 $73,435 Pending Closeout	Chee/ University of Western Australia	Characterizing Neo-Antigen T Cell Responses in Mesothelioma Immunity	RP: This study assessed the utility of neo-antigens of MM as targets for cancer immunotherapies. Results of this project show that immunotherapy checkpoint blockade treatment increases the number of neo-antigens, and that neo-antigen T cell response predicts outcomes to immunotherapy treatment. This suggests that neo-antigens could be used as a biomarker in mesothelioma patients. Results from this study will inform clinical trials utilizing neo-antigen information for vaccine development. MR: Compared to the general population, Active Duty Service members are at an increased risk for asbsestos exposure in shipyards, aircrafts, and other military occupations. In the United States, veterans account for nearly one-third of all MM diagnoses.	*Presentation: 1* *Publications: 2*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
MYELOPROLIFERATIVE DISORDERS				
CA140408 $453,875 Pending Closeout	Wilson/ University of New Mexico Health Sciences Center	Calreticulin and Jak2 as Chaperones for MPL: Insights Into MPN Pathogenesis	RP: This study tested 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 MPN. The understanding of pathogenesis, diagnosis, and treatment of MPNs will benefit military members.	*Publication: 1* *Presentations: 3* *Website: 1*
CA150767 $124,612 Pending Closeout	Ghaffari/ Icahn School of Medicine at Mount Sinai	Dual Inhibition of FLT3 and RET Pathways by ON150030 as Novel Strategy for AML Therapy	RP: This study aimed to test the therapeutic value of a new therapeutic agent, ON150030, for AML. MR: This novel agent could be used as an alternative therapy for Service members with AML who do not respond to the current treatment regimen.	*None to date*
NEUROBLASTOMA				
CA130153 $630,000 Pending Closeout	Freeman/ St. Jude Children's Research Hospital	The Development of a Primary Neural Crest Assay for Neuroblastoma Oncogenesis	RP: This study was conduted to rapidly screen for NB-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 military is partially determined by the health and welfare of their supportive families. Military missions benefit when Warfighters' families are healthy and well.	*Presentations: 5* *Publication: 1* *Miscellaneous: 1* *Funding Obtained: 1*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
NEUROBLASTOMA				
CA130396 $521,460 Pending Closeout	Stewart/ St. Jude Children's Research Hospital	Tumor Growth Model with PK Input for Neuroblastoma Drug Development	RP: This study aimed to develop a comprehensive computational tumor model using pharmacokinetic and pharmacodynamic measurements to predict drug response patterns in NB tumors. The PI constructed the proposed PBPK model using two NB therapeutics, and is testing the model's predictive capabilities. MR: The health and welfare of the military is partially determined by the health and welfare of their supportive families. Military missions benefit when Warfighters' families are healthy and well.	*Presentations: 4*
CA150773 $122,979 Pending Closeout	Qadeer/ Icahn School of Medicine at Mount Sinai	Investigating the Mechanisms Underlying ATRX Mutant Neuroblastoma	RP: In this study, the PI successfully validated a new technique for ATRX ChIP in NB cell lines. The PI used this novel technique to identify novel neurogenesis genes harboring significant ATRX peaks in wild-type NB cells. 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 NB, the PI aims to develop rational therapies to better manage the burden of disease.	*Presentation: 1* *Publication: 1*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
NEUROBLASTOMA				
CA150807 $113,636 Pending Closeout	Xu/ University of North Carolina at Chapel Hill	Exploiting Hypoxia for T-Cell Immunotherapy in Neuroblastoma	RP: Hypoxia is commonly associated with NB 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. In this study, the PI proposed that the proliferation differences are attributed to differential expression of hypoxia inducible factor 1-α (HIF1-α), and proposed to define the mechanisms of this differential expression. The PI also explored how this mechanism might be exploited to improve immunotherapy activity. MR: This project could lead to better and safer treatment options for NB, and will ultimately alleviate the physical and mental burdens of Active Duty Service members and their children who suffer from NB.	*Publication: 1*
PANCREATIC CANCER				
CA130229 $333,878 Closed	Brooks/ University of Mississippi	Novel Molecular Targets for KRAS Downregulation: Promoter G-Quadruplexes	RP: This study aimed to define the formation, regulation, and therapeutic potential of identified G-quadruplexes (G4s) within the K-RAS core promoter. The PI characterized the biophysical properties of G4 complexes within the K-RAS promoter, and conducted functional studies to describe how the G4 formations influence promoter activity. MR: Pancreatic cancer is one of the most lethal forms of cancer affecting Service members, veterans, military beneficiaries, and their families.	*Publication: 1* *Presentations: 10*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
PANCREATIC CANCER				
CA130578 $566,796 Closed	Tuveson/ Cold Spring Harbor Laboratory	The Early Detection of Pancreatic Cancer in the U.S. Military	RP: This study aimed to identify serological biomarkers during carcinogen-mediated pancreatic cancer initiation and progression upon exposure to military-relevant environmental carcinogens. After establishing the model systems, preliminary results identified several biomarker candidates that will be validated in future studies. MR: Pancreatic cancer is one of the most lethal forms of cancer affecting Service members, veterans, their families, and other military beneficiaries.	*Publications: 3* *Funding Obtained: 3*
CA140228 $531,685 Pending Closeout	Cukierman/ Institute for Cancer Research	Pancreatic Cancers Desmoplasia: The Possible Bridge Impending Nerve Infiltration and Neoplastic Escape	RP: This study was conducted to determine whether 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 that a lack of these proteins reduces neuronal cell growth. MR: Risk factors for pancreatic cancer, such as diabetes, poor diet, and smoking, are overrepresented among both Active Duty military personnel and veterans. This study will help close some of the gaps in diagnosis and treatment of military and veteran personnel.	*Publications: 4* *Funding Obtained: 2* *Computer Program/Software: 1* *Funding Applied for: 1* *Degrees Obtained: 1*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
PANCREATIC CANCER				
CA140634 $479,488 Pending Closeout	Stanger/ University of Pennsylvania	A Cell-Based Approach to Early Pancreatic Cancer Detection	RP: This study aimed to determine whether pancreatic cells circulating in the blood can be used as biomarkers to detect pancreatic cancer. To date, the PI 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: Currently, no test exists to diagnose pancreatic cancer at a stage early enough to affect interventions with the greatest likeliness to work. The creation of such a detection tool would greatly benefit military personnel.	*Publication: 1* *Miscellaneous: 2*
CA150842 $128,250 Pending Closeout	Patra/ Massachusetts General Hospital	Decoding Metabolic Programs Underlying Pancreatic Cancer Progression	RP: This study examined the metabolic alterations in pancreatic cancer cells with mutant GNAS and compared them to pancreatic cancer cells with other defined genetics. In particular, it aimed to study how mutations in the GNAS gene deregulate mitochondrial and lipid metabolism, and then to study how GNAS-regulated pathways drive alternative metabolic programs. MR: Pancreatic cancer is one of the most lethal forms of cancer affecting Service members, veterans, their families, and other military beneficiaries. This study could identify new therapeutic targets.	*Publications: 2* *Presentation: 1*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
PEDIATRIC BRAIN TUMOR				
CA130273 $522,410 Pending Closeout	Yun/ Jackson Laboratory	Cell of Origin and Cancer Stem Cell Phenotype in Medulloblastomas	RP: This study aimed to 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: The health and welfare of the military is partially determined by the health and welfare of its supportive families. Military missions benefit when the Warfighters' families are healthy and well.	*None to date*
CA130319 $331,063 Pending Closeout	Ying/ Hugo W. Moser Research Institute at Kennedy Krieger, Inc.	Modeling Aggressive Medulloblastoma Using Human-Induced Pluripotent Stem Cells	RP: This study determined that neural progenitors can be induced from human-induced pluripotent stem cells and form MYC-driven Group 3 MBs, 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 military is partially determined by the health and welfare of its supportive families. Military missions benefit when the Warfighters' families are healthy and well.	*Presentation: 1* *Funding Applied for: 3*
CA130436 $421,077 Pending Closeout	Hinchcliffe/ University of Minnesota, Twin Cities	Defects in Histone H3.3 Phosphorylation and ATRX Recruitment to Misaligned Chromosomes During Mitosis Contribute to the Development of Pediatric Glioblastomas	RP: This study 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 military is partially determined by the health and welfare of its supportive families. Military missions benefit when Warfighters' families are healthy and well.	*Publications: 2* *Presentations: 14* *Funding Obtained: 1* *Publications: 6*

Log Number/ Amount/Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
PEDIATRIC BRAIN TUMOR				
CA130562 $169,472 Closed (Early Termination)	Mulcahy Levy/ University of Colorado at Denver	Targeting BRAF V600E and Autophagy in Pediatric Brain Tumors	RP: This study found that inhibiting autophagy enhances the activity of BRAF inhibitors and may prevent acquired resistance to treatment in tumors. MR: The health and welfare of the military is partially determined by the health and welfare of its supportive families. Military missions benefit when the Warfighters' families are healthy and well.	*Funding Obtained: 1*
STOMACH CANCER				
CA150357 $196,971 Pending Closeout	Bao/ Brigham and Women's Hospital	Plasma Metabolomic Fingerprint of Early Gastric Cancer	RP: This study sought to describe the metabolomics fingerprint associated with gastric cancer. The PI measured 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, particularly for Service members who experience hazardous exposures to ionizing radiation. In addition, research has shown that Service members living under field conditions are at great risk of *H. pylori* infection, which is the main cause of gastric cancer.	*None to date*