FISCAL YEAR 2015
REPORT TO CONGRESS

U.S. ARMY MEDICAL RESEARCH AND MATERIEL COMMAND

CONGRESSIONALLY DIRECTED MEDICAL RESEARCH PROGRAMS

PEER REVIEWED CANCER RESEARCH PROGRAM

October 2016

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Peer Reviewed Cancer Research Program
Report to Congress

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BACKGROUND AND PURPOSE OF REPORT

BACKGROUND

The U.S. Army Medical Research and Materiel Command (USAMRMC) is a major subordinate Command of the U.S. Army Medical Command. The USAMRMC manages Army biomedical research and development programs and selected programs within the Department of Defense (DoD) Defense Health Program (DHP). As directed by the Office of the Assistant Secretary of Defense for Health Affairs (OASD[HA]), the DHA RDA Directorate manages the DHP Research, Development, Test, and Evaluation appropriation, including funds for the Peer Reviewed Cancer Research Program (PRCRP). The USAMRMC Congressionally Directed Medical Research Programs (CDMRP) manages the PRCRP in support of the OASD(HA) and the DHA RDA.

PURPOSE OF REPORT

The ASD(HA) has been directed to submit a report to the Congressional defense committees on the status of the PRCRP, and, for each research area, to include the funding amount awarded, the progress of research, and the relevance to Service members and their families. This report provides an update on the detailed status of the FY09-FY15 PRCRP, research accomplishments, and the relevance of PRCRP-supported research to U.S. military Service members and their families.

FY09-FY15 PEER REVIEWED CANCER RESEARCH PROGRAM

ESTABLISHMENT OF PRCRP

The PRCRP began in FY09 with a DoD appropriation as detailed in Tables 1 and 2. Each year during the PRCRP Vision Setting meeting, experts from the designated cancer fields (clinicians, scientists, active duty military oncologists, and consumers) convene to discuss the new Congressional language and respond to the knowledge gaps for the purpose of developing a new investment strategy that will both answer the Congressional call and compliment other federal agencies' research portfolios.

TABLE 1: PRCRP Appropriation and Topic Areas per Fiscal Year

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

*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.
†In FY09, the Congressional language designated specific funding amounts per topic area.
‡Award total represent the open, pending close-out, and closed awards, does not include withdrawals.

TABLE 2: PRCRP Topic Areas by Fiscal Year

Topic Area* (Appropriation)	FY09† ($16M)	FY10 ($15M)	FY11 ($16M)	FY12 ($12.8M)	FY13 ($15M)	FY14 ($25M)	FY15 ($50M)
Bladder cancer							
Blood cancers		✔	✔	✔	✔	✔	
Cancers related to radiation exposure						✔	
Colorectal cancer		✔	✔	✔	✔	✔	✔
Genetic cancer	✔	✔	✔	✔	✔	✔	✔
Immunotherapy							
Kidney cancer		✔	✔	✔	✔	✔	✔
Listeria vaccine for cancer		✔	✔	✔	✔	✔	✔
Liver cancer							✔
Lymphoma							
Melanoma and other skin cancers	✔	✔	✔	✔	✔	✔	✔
Mesothelioma			✔	✔	✔	✔	✔
Myeloproliferative disorders						✔	✔
Non-Invasive cancer ablation	✔						
Neuroblastoma					✔	✔	✔
Pancreatic cancer			✔	✔	✔	✔	✔
Pediatric brain tumors	✔	✔		✔	✔	✔	
Pediatric cancer			✔				
Radiation protection utilizing nanotechnology		✔	✔				
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.
†In FY09, the Congressional language designated specific funding amounts per topic area.

Awards granted in FY15 initiated research by 1 October 2016. Outcomes are expected by the end of the period of performance within 2 to 4 years of the start date of each award.

TOPIC AREA INVESTMENT

For each research topic area designated by Congress, the PRCRP has solicited pre-applications, invited full applications, and received, reviewed, and awarded full applications. Investment per Congressionally designated topic area is detailed in Table 3.

TABLE 3: Total Research Dollars Invested per Topic Area for FY15 and FY09-FY14

Topic Area	Total Dollars Recommended for Investment ($) FY15	Total Invested FY09-FY14 ($)
Blood cancer	0	13.2M
Cancers related to radiation exposure	0	0.9M
Colorectal cancer	4.1M	10.1M
Genetic cancer research[1,4]	1.7M	12.7M
Kidney cancer	1.3M	5.8M
Listeria vaccine for cancer[5]	0	0.8M
Liver cancer	9.2M	0
Melanoma and other skin cancers[2]	11.5M	17.9M
Mesothelioma	3.2M	3.8M
Myleoproliferative disorders	1.9M	0.5M
Neuroblastoma	1.9M	2.6M
Non-invasive cancer ablation[3]	0	1.8M
Pancreatic cancer	3.2M	9M
Pediatric cancer	0	0.8M
Pediatric brain tumors	0	6.9M
Radiation protection utilizing nanotechnology	0	0
Stomach Cancer	7.7M	0
Total Research Investment[6]	**45.7M**	**86.8M**

[1]Topic area includes FY09 Congressional language: Genetic cancer and its relation to exposures to the various environments that are unique to the military lifestyle and the FY10 Congressional language: Genetic cancer research and genomic medicine.
[2]Topic area includes FY09 Congressional language: Melanoma and other skin cancers as related to deployments of Service members to areas of high exposure and the FY10 Congressional language: Melanoma and other skin cancers.
[3]Non-invasive cancer ablation treatment including selective targeting with nanoparticles.
[4]No applications met the intention and scope of the program announcement for recommendation for funding.
[5]No full applications were submitted for this topic area.
[6]Total investment in research dollars is less USAMRMC and CDMRP management costs (~12%) and FY12 and FY13 sequestration costs ($2,131,000).

PRCRP MILITARY FOCUS

Since its inception, the PRCRP has focused its vision to improve the quality of life by decreasing the impact of cancer on Service members, their families, and the American public.

As a funding program, the most significant method the PRCRP has to influence the quality of life and well-being of Service members and their families is through the creation of impactful funding opportunities that emphasize the health and well-being of this community. In FY13, the PRCRP introduced a new program announcement/funding opportunity, the *Idea Award with Special Focus*. The *Special Focus* targeted specific issues and critical threats to the health and well-being of Service members and their families. The *Special Focus* also refers to the required Military Relevance Focus Areas that applicants must respond to in the pre-application and the full application.

To address the cancer health needs of both deployed and non-deployed personnel, their dependents, retirees, and Veterans, the PRCRP seeks to support studies that are responsive to the FY15 Military Relevance Focus Areas listed below:

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

In addition to the *Idea Award with Special Focus* in FY15, the PRCRP answered unmet needs in understanding critical clinical outcomes for Service members, their families, and the American public through the *Translational Team Science Award* that leverages information from ongoing or completed clinical trials funded through other agencies to address knowledge gaps and move these observations toward clinical application. Gap analysis has revealed that understanding clinical trial outcomes and supporting correlative studies are crucial to the development and translation of trial results toward productive bedside outcomes. To fill this important niche, the PRCRP utilizes the *Translational Team Science Award* to bring together research on an overarching clinical outcome with special emphasis on the military relevance focus areas and on collaborations with Department of Veterans Affairs (VA) or military researchers.

At the second tier of the review process, the programmatic review, the Programmatic Panel members weigh the military relevance of each application. Applications that addressed exposures, conditions, or circumstances that are unique to the military, or disproportionately represented in a military beneficiary population, are the highest priority for the program. Through innovative funding mechanisms, the PRCRP is poised to continue to serve all military beneficiaries, including Service members and their families.

CANCER RESEARCH RELEVANCE: SERVICE MEMBERS AND THEIR FAMILIES

The PRCRP is charged with the task of funding research that would improve the quality of life by decreasing the impact of cancer on Service members, their families, and the American public. The VA has acknowledged that certain exposures may increase the cancer risk of Service members and their families.

Environmental hazards can increase the risk of cancer development. Members of the military are exposed to hazardous environments at home and during deployments due to the nature of their service.[1] Exposure related to cancer risks include but are not limited to chemical weapons, or storage, ionizing radiation, herbicides, electromagnetic fields, jet fuel, organic materials, biological agents, ultraviolet radiation, etc., have been linked to different malignancies (Table 4).

TABLE 4: Malignancies Associated with Military Service[ii]

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

[ii]Antonic, V., et al,. 2013. *J. Cancer* 4:227-240.; Center for Disease Control and Prevention, http://www.cdc.gov/hpv/cancer.html; Crawford, R.S., et al., 2007. *Mil. Med.* 172:1084-1088.; Dalanger, N.A., et al., 1995 *J. Occup. Environ. Med.* 37:298-305.; Department of Defense Automated Central Tumor Registry.; D'Este, C., et al., 2008. *Am. J. Ind. Med.* 51:16-23.; Eneworld, L.R., et al., 2012. *Cancer* 118:1397-1402. Enewold, L.R., et al., 2011. *Cancer Epidemiol. Biomarkers Prev.* 20:2369-2376.; Lea, C.S., et al., 2014. *Mil. Med.* 179:247-253.;Piazuelo, M.B., et al., 2010. I*nfect. Dis. Clin. North Am.* 24:853-869.; Powers, J. et al., 2014. Presentation *World Congress on Cancer of the Skin.*; The Selected Cancers Cooperative Study Group., 1990. *Arch. Intern. Med.* 150:2473-2483.; U.S. Department of Veteran's Affairs, Public Health http://www.publichealth.va.gov/exposures/index.asp, http://www.infectagentscancer.com; VHA-Directive, 2003-34; Zhu, K., et al., 2009., C*ancer Epidemiol. Biomarkers Prev.* 18:1740-1745.; Zullig, L.L., et al., 2012., *Mil. Med.* 177:693-70

Detailed analysis by the Automated Central Tumor Registry of DoD-published data demonstrated that the incidence of melanoma was higher in the U.S. military population in comparison to the U.S. general population.[2] Lea, et al., reported that the incidence rates of melanoma in active duty military personnel were higher than the population-based registry in the United States.[3] This study showed that Air Force personnel had the highest incidence rates of melanoma in the military. With these outcomes in mind, the long-term risk of cancer

development for Service members deployed to areas of high ultraviolet exposures, especially melanoma as one of the deadliest forms of skin cancer, must be acknowledged. The Senate Appropriations Committee on Defense for FY16 acknowledged that melanoma diagnoses are increasing in Service members and that it is the fifth most common cancer among Veterans due to the exposures to areas of high ultraviolet radiation. A recent study showed that incident diagnosis in the U.S. Armed Forces linked age with an increased risk of cancer, thus showing that Veterans have the highest burden of risk.[4] Additionally, the Senate Appropriations Committee on Defense noted that recent studies suggest that exposures to high levels of solar radiation may be associated with a higher mortality risk in melanoma. The Committee has encouraged investments in melanoma research to combat this cancer risk (DoD SAC-D 114-63, 2016, page 207).

The PRCRP has invested over $29.4M in melanoma and other skin cancers research. A paradigm shifting study by Brash, et al.,[5] funded by the PRCRP showed that ultraviolet (UV) radiation caused cancer risk to continue long after the solar radiation exposure ends due to the skin type and intercellular free radical cascade. Through the same study, Dr. Brash and colleagues discovered how to quench the free radical cascade, thus decreasing further DNA damage and answering an unmet gap in melanoma prevention.

Congress has tasked the PRCRP to answer unmet biomedical research needs of our military on several occasions including events such as the Fukushima disaster in Japan and the resulting potential radiation contamination. In FY14, Congress added the topic area cancer related to radiation exposure to the PRCRP. This resulted in funding in this topic area of nearly $1M for two FY14 Idea Awards with Special Focus. Both studies were awarded in September 2015 and the research is underway. In brief, Dr. Nelson Chao, M.D., of Duke University is studying a novel therapeutic target for radiation induced hematological malignancies. Exposure to radiation can transform hematopoietic stem cells, immature cells that develop into different types of specialized blood cells. These transformed cells evade the immune system and may become malignant. Using mouse models, Dr. Chao is working on verifying the effects of protein deletion due to radiation exposure on lymphoma and myeloma progression. Additionally, Dr. Chao's team is testing whether an identified inhibitor represents a new class of therapeutics that could cure radiation induced blood cancer. In the second study, Dr. Mohan Natarajan of the University of Texas Health Science Center at San Antonio is researching how radiation exposure causes oxidative stress. Dr. Natarajan is investigating how radiation exposure alters free radical signaling in a model of blood vessels, since they are the tissues most susceptible to radiation. Specifically, he is testing how altered signaling effects two cellular pathways—K-ras and estrogen receptor—often associated with tumor initiation and progression. Both of these awards demonstrate the focus of the PRCRP to discover how the potent risk for cancer development might be mitigated through identification of biological weaknesses to radiation stress and novel therapeutic targets.

The investigation into multiple cancer risks and military service include the study of specific chemical exposures (e.g., pesticides, fuels, environmental carcinogens). Hodgkin's disease is one of the most common cancer diagnoses in men who served in the U.S. Navy. The Selected Cancers Cooperative Study Group showed that Veterans of the Vietnam War had a 50% increase in risk of Hodgkin's disease as compared to subjects who had not served in Vietnam.[6, 7]

Evidence links an increased risk for soft tissue sarcomas, non-Hodgkin's lymphoma, Hodgkin's disease, and chronic lymphocytic leukemia to Vietnam War service and exposure to herbicides such as Agent Orange.[8] Additionally, the U.S. Congress has tasked the Institute of Medicine to deliver a report on the health effects of Agent Orange every 2 years. The latest report[9] titled *Veterans and Agent Orange: Update 2014*, analyzed the herbicide and cancer risk showing that there is sufficient evidence of an association with exposure and cancer development for soft tissue sarcomas, non-Hodgkin lymphoma, Hodgkin disease, chronic lymphocytic leukemia and that there is suggestive evidence for an association with the development of cancers including lung, prostate, bladder, and multiple myeloma.

Militarily relevant exposures to solvents and other environmental pollutants have been linked to increased mortality and hazard ratios for cancers including kidney, liver, esophageal, cervix, multiple myeloma, and Hodgkin's disease.[10] The retrospective study evaluated solvents as pollutants in drinking water at Camp Lejeune leading to a link in elevated death hazard ratios for the identified cancers. In addition, studies of common military exposures, such as aircraft maintenance, have been associated with an increased risk of cancer.[11]

Another hazardous exposure includes asbestos, a known carcinogen, causing cancers such as mesothelioma, lung cancer, cancer of the larynx, and other cancers including cancers of the pharynx (throat), stomach, colon, and rectum (http://www.cancer.org/cancer/cancercauses/othercarcinogens/intheworkplace/asbestos). Asbestos-related diseases such as mesothelioma are a known risk to Naval shipyard work.[12] It is generally accepted that nearly 95% of all mesothelioma cases are due to asbestos exposure. While utilization of exposed asbestos as a building material in the United States has declined, many countries where our Service members are deployed still rely on asbestos as a major material for housing and building manufacturing.[13] Dr. Haining Yang from the University of Hawaii, funded by a PRCRP Career Development Award, discovered molecular triggers and endogenous genetic alterations that increase the risk of cancer following low dose asbestos exposures. Dr. Yang's study identified key genetic components that would increase an individual's risk with respect to the amount of asbestos exposure. Additionally, leveraging her results and outcomes, she has been awarded two new grants totaling over $1M. Her continued dedication into studying asbestos-related cancers and finding therapeutics for mesothelioma (a cancer with a survival rate of less than 1 year after diagnosis) supports the relevant focus area of carcinogens and cancer risk during military service.

Chemical agents are not the only hazards Service members might encounter during deployments. Many deployments are to developing countries where there may be a higher incidence of infectious vectors. Infectious diseases have been linked to cancer genesis. Yamane reported that the most frequent cancers diagnosed in Air Force Service members between 1989 and 2002 were different from the general U.S. population, with a higher[14, 15, 16] incidence of melanoma, testicular, thyroid, cervical, and vulvar cancers,[14] particularly cervical and vulvar cancer. It is estimated that over 18% of cancers, such as gastric adenocarcinoma, cervical carcinoma, and hepatocarcinoma, may be a result of infections.[17] Service members are increasingly presenting with sero-positive scores for infectious agents such as *Helicobacter pylori.*[18] These Service members may be more at risk for chronic inflammation and the development of cancers of the gastrointestinal tract.

Cancer patterns change as demographics change in the military. As the configuration of the military population changes to include more women, consideration into research on their risks and exposures is critical. Cancer patterns of Vietnam War military women nurses in comparison to non-Vietnam War military women nurses and the general population showed that site-specific cancer patterns were different, with excess deaths from pancreatic and uterine corpus cancers in the Vietnam War military women nurses.[19] A recent study by Fastje, et al.,[20] and funded by the PRCRP, showed that *in utero* exposure to tungsten and other environmental agents primed the immune system for aberrant responses to infectious agents and could lead to increased carcinogenic risk. Additionally, transgenerational effects of occupational exposures may lead to increased risk of cancer development in progeny. Children of Vietnam War Veterans have an increased risk of developing acute myeloid leukemia.[8] As shown by Hicks et al.,[23] children of men in the Air Force had a higher incidence of tumors of the central nervous system (brain and spinal cord) and lymphatic system. The Veterans Health Administration (VHA) acknowledged the toll of cancer on Service members and their families when releasing its National Cancer Strategy in 2003 (VHA-Directive 2003-34).

Indirect risk factors for cancer development are also under investigation. Two studies funded by the PRCRP recently published results that linked higher stress to increased cancer risk.[21, 22] Chronic stress murine models revealed an important link to attenuation of p53 (a tumor suppressor) and tumorigenesis.[21] Another study demonstrated the potent effect of neuropeptides and other stress mediators on tumor development and progression.[22] Stress and related issues are a concern for the military and may impact the ultimate health and well-being of Service members both during and after deployment.

The incidence and risk of cancer in the military is still under investigation. The Congressional directive for the PRCRP is to fund meritorious research for the benefit of Service members and their families and to continue a tradition of improving the quality of life for those impacted by a cancer diagnosis.

PRCRP RESEARCH PROGRESS

SELECTED RESEARCH ACCOMPLISHMENTS

The PRCRP has recommended a total of 114 awards for FY15 funding. The military relevance and research progress of all open awards (awards where the period of performance has not expired) can be found in Table 5. Selected highlights of funded awards are listed by topic area with references and links below:

BLOOD CANCER

Michaela Reagan, PhD, Dana-Farber Cancer Institute

Improved models of how multiple myeloma (MM) progresses in the bone marrow are urgently needed to facilitate the development and clinical translation of MM inhibitors. Dr. Reagan developed a novel cell culture model based on a silk-protein scaffold that better mimics tumor growth in the bone than traditional culture models. This new model was used to study how MM grows in a bone marrow-like environment and how MM impairs bone growth. She identified the

first microRNA (miR), a short regulatory nucleic acid, abnormally expressed in bone cancer patients. Targeting this miR could lead to therapeutics that enhance bone healing to fight cancer induced bone disease and potentially reduce tumor burden. Dr. Reagan is now more fully elucidating the effects of bone cells on cancer cells in her new independent laboratory at the Maine Medical Center. Dr. Reagan's work is important for MM, a disease particularly relevant to our Veterans. Male Veterans using VA hospitals are at 51% increased risk of MM compared to the general public.

Swami A, Reagan MR, Basto P, Mishima Y, Kamaly N, Glavey S, Zhang S, Moschetta M, Seevaratnam D, Zhang Y, Liu J, Memarzadeh M, Wu J, Manier S, Shi J, Bertrand N, Lu ZN, Nagano K, Baron R, Sacco A, Roccaro AM, Forokhzad OC, and Ghobrial IM. 2014. *Proc Natl Acad Sci U S A* 111(28):10287-10292.
Reagan MR, Mishima Y, Glavey SV, Zhang Y, Manier S, Lu ZN, Memarzadeh M, Zhang Y, Sacco A, Aljawai Y, Shi J, Tai YT, Ready JE, Kaplan DL, Roccaro AM, and Ghobrial IM. 2014. *Blood* 124(22):3250-3259.

COLORECTAL CANCER

Sivanesan Dakshanamurthy, PhD, Georgetown University

Dr. Dakshanamurthy is developing novel *in-silico* methods to identify cellular pathways adversely affected by environmental chemicals to which members of our military may be exposed during their service. In collaboration with Dr. Stephen Byers, he plans to use this information to explain how these interactions are important in the formation of colorectal cancer.

John Jessup, MD, National Cancer Institute

Dr. Jessup demonstrated that the NANOGP8 gene directly modulates and maintains stem cell characteristics of colorectal carcinoma (CRC) cells. Furthermore, he used a lentiviral vector delivered short hairpin RNA (shRNA), an artificial RNA, in human CRC cells to show that the transduction of shRNA targeting NANOGP8 induces apoptosis and inhibits further cell proliferation. Unfortunately, when Dr. Jessup tested the shRNA in human CRC growing in mice, the shRNA had only a transient effect on slowing tumor growth. He and his colleagues then developed an adenovirus that contains the shRNA and grows preferentially in human CRC cells, and he demonstrated that this continuously inhibits the growth of large human CRC tumors in mice. These findings could help improve drug activity and provide a new route in therapy regimens for CRC. Approximately 50% of military personnel and dependents who are diagnosed with colon or rectal carcinoma will die of the disease. Dr. Jessup's research focuses on the growth of established human colorectal xenografts in preclinical models, which will benefit military personnel and dependents once it has matured into a clinical treatment.

Mattoo AR, Zhang J, Espinoza LA, and Jessup JM. 2014. *Clin Cancer Res* 20(21):5446-5455.
Zhang J, Espinoza LA, Kinders RJ, Lawrence SM, Pfister TD, Zhou M, Veenstra TD, Thorgeirsson SS, and Jessup JM. 2013. *Oncogene* 32(37):4397-4405.

GENETIC CANCER

Robert L. Moritz, PhD, Leroy Hood, MD, PhD, Gregory Folz, MD, PhD, and Charles Cobbs, MD, Institute for Systems Biology and the Swedish Neuroscience Institute

Drs. Moritz, Hood, Folz, and Cobbs have developed techniques in proteogenomic analysis for whole-genome sequencing of cancer patients' tumors, individual tumor cells, non-cancerous cells, and non-cancerous cells from the patients' family members to perform inheritance analysis

and identify candidate genes involved in neoplastic glioblastoma formation. These techniques, combined with proteomic analysis tools, have led to the identification of perturbed networks of genes, providing promising insights for the discovery of novel targeted therapeutics for glioblastoma and identification of novel blood biomarkers for early detection. Identification of biomarkers for early detection of cancer answers an unmet gap in the cancer care spectrum and, therefore, supports the long-term health and well-being of military beneficiaries.

Roach JC, Glusman G, Smit AF, Huff CD, Hubley R, Shannon PT, Rowen L, Pant KP, Goodman N, Bamshad M, Shendure J, Drmanac R, Jorde LB, Hood L, and Galas DJ. 2010. *Science* 328(5978):636-639.
Li XJ, Hayward C, Fong PY, Dominguez M, Hunsucker SW, Lee LW, McLean M, Law S, Butler H, Schirm M, Gingras O, Lamontagne J, Allard R, Chelsky D, Price ND, Lam S, Massion PP, Pass H, Rom WN, Vachani A, Fang KC, Hood L, and Kearney P. 2013. *Sci Transl Med* 5(207):207ra142.

KIDNEY CANCER

Muneesh Tewari, MD, PhD, Fred Hutchinson Cancer Research Center, Allan Pantuck, MD, University of California, Los Angeles

Dr. Tewari and Dr. Pantuck are using a novel technology of droplet digital PCR (ddPCR) with high precision and sensitivity to identify and evaluate miR-210, a circulating regulatory fragment of RNA, called miRNA, as a blood-based biomarker for clear cell renal carcinoma. They studied and have reported in detail the sensitivity and reproducibility of the ddPCR method for measuring miR-210 and other plasma biomarkers. They hope that miR-210 can be used as a diagnostic tool in blood-based early detection of clear cell kidney cancer. The third most common urological diagnosis at the VHA system are renal masses; thus, research that helps to find these masses earlier will benefit military beneficiaries.

Hindson CM, Chevillet JR, Briggs HA, Gallichotte EN, Ruf IK, Hindson BJ, Vessella RL, and Tewari M. 2013. *Nat Methods* 10(10):1003-1005.

LISTERIA VACCINE FOR CANCER

David Chung, MD, PhD, Memorial Sloan Kettering Cancer Center

A promising approach to cancer treatment is to make vaccines using specialized cells of the immune system called dendritic cells. Dr. Chung found that a noninfectious strain of *Listeria monocytogenes* bacteria could activate dendritic cells while avoiding excessive activation of immune-dampening factors that could impede vaccine responses. These results support the use of Listeria to boost dendritic cell vaccine efficacy. The insight gained from this project could be used to develop cancer vaccines for multiple cancers that are prevalent among our Service members, Veterans, and their families.

Chung DJ, Romano E, Pronschinske KB, Shyer JA, Mennecozzi M, St. Angelo ET, and Young JW. 2013. *J Transl Med* 11:166-175.

MELANOMA AND OTHER SKIN CANCERS

Douglas Faller, MD, PhD, Boston University Medical Campus

Dr. Faller used a small molecule inhibitor of the signaling Protein Kinase Cδ (PKCδ) for specific targeting of melanoma with mutations in the NRAS gene and melanomas that have developed resistance to therapeutic inhibitors of BRAF. The PKCδ inhibitor lead compound has been

refined for potency and specificity. Studies are ongoing to optimize a "final" compound that will be tested for clinical relevancy using a mouse melanoma model. Military Service members are at greater risk for the development of melanoma due to increased sun exposure. As the incidence of melanoma has increased in recent years, Dr. Faller's research aims to develop a targeted and effective therapeutic approach to treat melanoma.

Chen Z, Forman LW, Williams RM, and Faller DV. 2014. *BMC Cancer* 14:90-98.
Takashima A, English B, Chen Z, Cao J, Cui R, Williams RM, and Faller DV. 2014. *ACS Chem Biol* 9(4):1003-1014.

Daniel Bikle, MD, PhD, Northern California Institute for Research and Education

Many of our Service members are currently stationed in areas of the world where sunlight exposure is intense, and their duties often require long periods of exposure to the sun. Dr. Bikle's work aims to determine if vitamin D can play a role in preventing the development of skin cancers. He has demonstrated that, following acute UVB exposure, there is delayed clearance of specific indicators of DNA damage in vitamin D receptor (VDR) knockout mice. These novel data indicate that VDR plays an important role in facilitating DNA damage repair, and any damage not repaired could potentially lead to the formation of melanoma or non-melanoma skin cancers.

Bikle DD and Jiang Y. 2013. *Cancers (Basel)* 5(4):1426-1438. doi: 10.3390/10cancers5041426.

MESOTHELIOMA

Ravi Salgia, MD, PhD, University of Chicago

Dr. Salgia targeted malignant pleural mesothelioma (MPM) with a trio of small molecule inhibitors that block three cellular signaling molecules: MET receptor tyrosine kinase, phosphatidylinositol 3-kinase (PI3K), and mammalian target of rapamycin (mTOR). The combined use of these inhibitors was more effective than using any single drug in suppressing MPM cell motility and growth in vitro, and tumor growth in an in vivo mesothelioma mouse model. Many of our military personnel are exposed to asbestos, the most significant risk factor for mesothelioma development, while serving in developing countries or in Navy shipyards. Dr. Salgia's studies show promise in the development of a novel and effective treatment for mesothelioma.

Kanteti R, Dhanasingh I, Kawada I, Lennon FE, Arif Q, Bueno R, Hasina R, Husain AN, Vigneswaran W, Seiwert T, Kindler HL, and Salgia R. 2014. *PLoS One* 9(9):e105919. doi: 10.1371/journal.pone.0105919.

MYELOPROLIFERATIVE DISORDERS

Bridget Wilson, PhD, University of New Mexico Health Sciences Center

Drs. Wilson and Cleyrat are applying state-of-the-art techniques to define the interactions between three proteins (Mpl, Jak2, and calreticulin), which are key to the development of myeloproliferative neoplasm (MPN). This research could lead to preclinical studies that translate this mechanistic information into new therapeutic strategies for MPN patients, which include Service members, who are at increased risk for developing MPN.

NEUROBLASTOMA

Clinton Stewart, PharmD, St. Jude Children's Research Hospital

The health and welfare of our Service members is partially determined by the health and welfare of their families. Missions benefit when the Service members' families are healthy and well. Dr. Stewart is building a novel pharmacokinetic model with an individualized tumor compartment and 3D drug transport model to better understand and quantify chemotherapeutic uptake in neuroblastoma tumors. This model will more accurately predict drug effect within the 3D geometry of individual neuroblastoma tumors. Completion of this model will allow clinicians to make more informed decisions on treatment dosing and scheduling.

NON-INVASIVE ABLATION

Anthony Berdis, PhD, Case Western Reserve University

Technological advances supported by the military increase the ability of caretakers to answer the needs of Service members and their families. Over the course of this award, Dr. Berdis synthesized several novel gold-containing anti-cancer agents and demonstrated that these compounds could reduce cancer growth, with minimal signs of toxicity, when combined with clinically relevant doses of ionizing radiation. This combination could provide a new strategy to noninvasively ablate tumors.

Craig S, Gao L, Lee I, Gray T, and Berdis AJ. 2012. *J Med Chem* 55:2437-2451.

PANCREATIC CANCER

Pinku Mukherjee, PhD, University of North Carolina at Charlotte

Dr. Mukherjee observed that MUC1-overexpressing pancreatic cancer cells (>80% of pancreatic ductal adenocarcinomas) also express high levels of proteins that induce angiogenesis and metastasis, namely, Neuropilin-1 (NRP1) and vascular endothelial growth factor (VEGF), which interact with each other within the tumor microenvironment. She demonstrated that by blocking the interaction of NRP1 and VEGF, tumor burden was reduced in MUC1-overexpressing pancreatic tumors. Certain behavioral risk factors, such as smoking and the consumption of alcohol, are known to increase the chances of developing pancreatic cancer. Dr. Mukherjee's research provides insight into the molecular mechanisms that contribute to the aggressive and deadly nature of pancreatic cancer.

Zhou R, Curry JM, Das Roy LD, Grover P, Haider J, Moore LJ, Wu ST, Kamesh A, Yazdanifar M, Ahrens WA, Leung T, and Mukherjee P. 2016. *Oncogene* (Epub ahead of print). doi: 10.1038/onc.2015.516.

PEDIATRIC BRAIN TUMORS/PEDIATRIC CANCER

Oren Becher, MD, Duke University

Dr. Becher identified the transcription factor Pax3 as differentially expressed between cortical gliomas and brainstem gliomas, including diffuse intrinsic pontine glioma (DIPG). DIPG afflicts the pediatric population and is the leading cause of death for children with brain tumors. Expression of the Pax3 transcription factor enhances the growth and survival of murine brainstem glioma cells and is increased in 40% of human DIPGs, results that provide a novel marker with which to characterize and subtype the disease. These findings increase our

understanding of DIPG classification and are important for the development of targeted therapeutics.

Misuraca KL, Barton KL, Chung A, Diaz AK, Conway S, Corcoran DL, Baker SJ, and Becher OJ. 2014. *Acta Neuropathologica Communications* 2(1):134.

Patrick Paddison, PhD, Fred Hutchinson Cancer Research Center

Dr. Paddison performed multiple genome-wide RNAi screens in patient derived glioblastoma multiforme stem cells (GSCs) and discovered that the plant homeodomain finger domain protein PHF5A is required for GSC expansion. Additional studies revealed another protein, PKMYT1, as necessary for GSC viability. Both PHF5A and PKMYT1 are novel candidate drug targets for adult and pediatric glioblastoma tumors.

Toledo CM, Ding Y, Hoellerbauer P, Davis RN, Basom R, Girard EJ, Lee E, Corrin P, Hart T, Bolouri H, Davison J, Zhang Q, Hardcastle J, Aronow BJ, Plaisier NS Moffat J, Lin Q, Li XN, Nam DH, Lee J, Pollard SM, Zhu J, Delrow JJ, Clurman BE, Olson JM, and Paddison PJ. 2015. *Cell Reports* 13(11):2425-2439.
Hubert CG, Bradley RK, Ding Y, Toledo CM, Herman J, Skutt-Kakaria K, Girard EJ, Davison J, Berndt J, Corrin P, Hardcastle J, Basom R, Delrow JJ, Webb T, Pollard SM, Lee J, Olson JM, and Paddison PJ. 2013. *Genes Dev* 27(9):1032-1045.

Xuanming Shi, PhD, University of Texas Southwestern Medical Center

Overactive Sonic hedgehog (Shh) signaling in cerebellum granular neural precursor (CGNP) is the leading cause of childhood medulloblastoma (MB). Dr. Shi identified Brg1, a chromatin remodeler required to express the target of oncogene Shh. He observed Brg1 was integral in CGNP and tumor cell proliferation. Through deletion of Brg1, he demonstrated inhibition of MB progression via a reduction of mitogenic target genes and tumor cell proliferation.

Shi X, Wang Q, Gu J, et al. 2016. *Oncogene* (in press).
Shi X, Zhang Z, Zhan X, Cao M, Satoh T, Akira S, Shpargel K, Magnuson T, Li Q, Wang R, Wang C, Ge K, and Wu J. 2014. *Nature Commun* 5:5425.

The work of Drs. Becher, Paddison, and Shi represents an important area of study for the health and well-being of military families. In order to support active duty Service members and ensure a fit force, the military members' families must be healthy as well.

SUMMARY OF RELEVANCE AND PROGRESS OF PRCRP AWARDS

Table 5 includes a summary of all open awards as of 31 July 2016. The log number, topic area, last name of Principal Investigator (PI), award amount, institution, title, research progress, and military relevance are noted for each award. For information on closed awards (awards where the period of performance has expired), see Appendix A.

SUMMARY

A healthy family unit, free of serious illnesses, allows the Service member to focus on his or her role as a Warfighter and facilitates the overarching military mission. There are over 300,000 military beneficiaries with a cancer diagnosis, for a prevalence of 4.1%, comprised of over 60 different cancer types.[24] The cost of cancer care within the Military Health System in FY02 was over $1 billion.[24] Funding studies on the detection, diagnosis, treatment, and prevention of these

diseases benefits both the Warfighter and the American public, ultimately leading to increased survival rates and decreased costs of medical care.

TABLE 5: Research Project and Military Relevance of Under Negotiations (Under Neg), 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
Blood Cancer				
CA120064 $308,400 Open	Brander/ Duke University	Understanding Drug Resistance to Targeted Therapeutics in Malignant B-Cell Lymphoproliferative Disorders	RP: Seeks to determine mechanisms for drug resistance in chronic lymphocytic leukemia and to define the role of the microenvironment in drug resistance to targeted small molecule inhibitors. MR: This study will potentially advance the care of military patients with leukemia.	*Presentations: 11* *Funding obtained: 2 grants*
CA120128 $399,600 Open	Halene/ Yale University	Assessing the Mechanisms of MDS and Its Transformation to Leukemia in a Novel Humanized Mouse	RP: Development of a humanized mouse model for myelodysplastic syndrome (MDS) and study of the kinetics of progression of MDS to leukemia in vivo. MR: Myelodysplasia and leukemia affect military personnel with normal aging or with exposure to genotoxic agents.	*Presentations: 3*
CA120212 $417,600 Open	Cheloufi/ Massachusetts General Hospital	Investigating Epigenetic Parallels between Carcinogenesis and Reprogramming to Pluripotency	RP: Identification of the epigenetic regulators of somatic cell reprogramming to pluripotent stem cells and characterization of the common molecular traits of cancer cells and induced pluripotent stem cells. MR: The study has a broad impact on the understanding of cancer development and identification of novel cancer drug targets, which will lead to a better quality of life for Service members and their families.	*Presentation: 1* *Funding obtained: 1 grant* *Publication: 1*

Log Number/ Amount/ Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Blood Cancer				
CA120381 $383,998 Open	Reshef/ University of Pennsylvania	Chemokine Receptor Signatures in Allogeneic Stem Cell Transplantation	RP: To determine the role of chemokine receptor expression in regulating the organ distribution of effector T-cells after stem cell transplantation-associated graft-versus-host-disease, and to determine the effect of targeted chemokine receptor blockade on trafficking patterns of T-cell clones. MR: Graft-versus-host disease is a major cause of morbidity and mortality in allogeneic stem cell transplantation in treatment of blood cancers.	*Presentations: 2* *Funding obtained: 3 grants*
CA130124 $362,178 Open	Magee/ Washington University	Temporal Changes in FLT3-ITD Regulation of Stem Cell Self-Renewal and Leukemogenesis	RP: To test whether a receptor tyrosine kinase FLT3-ITD depletes hematopoietic stem cells; to test whether fetal and adult hematopoietic progenitors have different FLT3-ITD-driven signal transduction mechanisms and gene expression; and to test whether ectopic Lin28b expression impedes FLT3-ITD-driven depletion and leukemogenesis. MR: Service members have more risks for being exposed to mutagens than civilians; therefore, it is important to understand how the developmental history of a given leukemia will influence its genetic makeup and response to therapy.	*Presentations: 3*
CA130155 $482,404 Open	Atchison/ University of Pennsylvania	YY1 Control of AID-Dependent Lymphomagenesis	RP: To study the role of the transcription factor YY1 in B-cell lymphomagenesis or disease progression. MR: Vietnam War Veterans have a greatly increased risk of Hodgkin's lymphoma (HL), non-Hodgkin's lymphoma (NHL), and chronic lymphocytic leukemia, and many of these cancers initiate due to activation-induced cytidine deaminase activity. Additionally, children of Vietnam War Veterans have an increased risk of developing acute myeloid leukemia.	*None to date*

Log Number/ Amount/ Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Blood Cancer				
CA130247 $534,407 Open	Wang/ University of North Carolina at Chapel Hill	Epigenetic Therapy of Hematopoietic Malignancies: Novel Approaches for Tissue-Specific and Global Inhibition of EZH2 Enzymatic Activities	RP: To develop novel means to target two novel proteins of B-cell derived tumors for anticancer therapies and to investigate the mechanism by which these proteins induce B-cell-related tumors. MR: Blood cancers, including lymphoma and multiple myeloma, are associated with exposure to chemical and biological agents from the Vietnam and Gulf Wars.	*Publications: 3*
CA130256 $364,538 Open	Lapalombella/ Ohio State University	Understanding and Targeting the Nuclear Export Protein XPO1 in B-Cell Malignancies	RP: To determine the effects of the XPO1 mutations on the development and pathogenesis of chronic lymphocytic leukemia (CLL). MR: CLL is more prevalent in Veterans, particularly in those who served during the Vietnam War due to the exposure to Agent Orange and other toxins.	*Publication: 1* *Degree/Employment: Obtained a faculty position* *Funding obtained: 3 grants*
CA130371 $270,365 Open	Cardelli/ Louisiana State University Health Sciences Center	Exploring Potential Link between Bacterial Flora, Myeloid-Derived Suppressor Cells (MDSC), and Extraintestinal Tumor Development	RP: To test if germ-free mice will show reduced tumor growth and enhanced anti-tumor immune response. MR: Military members and their families are exposed to a variety of environmental pollutants, which increases their risk of certain cancers. Frequent changes in geographical locations, accompanying changes in diet, and exposure to environmental pollutants can alter the microbiome in military personnel more profoundly than that of the general public.	*None to date*

Log Number/ Amount/ Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Blood Cancer				
CA130445 $465,000 Open	Jamieson/ University of California San Diego	Identification of Novel RNA Editing Biomarkers of Human Leukemia Stem Cell Generation	RP: To test the hypothesis of whether foreign nucleic acid sensing and editing pathways, such as ADAR1, are activated during acute myeloid and lymphoid leukemia propagation as a result of retention of viral genetic material in dormant stem cells. MR: This research will broaden our understanding of risk factors for blood cancer progression and therapeutic resistance in military personnel. New therapeutic strategies could be designed to protect against carcinogenic infectious agents in military environment.	*Publication: 1* *Presentations: 26* *Patents: 1 invention report, 1 PCT patent application* *Funding obtained: 5 grants*
CA140119 $556,200 Open	Ji/ Northwestern University	The Role of mDia1 in the Aberrant Innate Immune Signaling in del(5q) Myelodysplastic Syndromes	RP: Deletion of chromosome 5 long arm (del(5q)) is the most common genetic defect in patients with MDS. This study is to test the hypothesis that mDia1 deficiency induces aberrant innate immune signaling that is critical for the pathogenesis of del(5q) MDS. MR: Pathogen-associated molecular patterns or damage-associated molecular patterns resulted from military deployment could trigger abnormal immune responses that lead to MDS.	*New research – no outcomes reported to date*
CA140236 $610,200 Open	Fontan/ Cornell University Weill Medical College	Nuclear Functions of BCL10 and MALT1 and Their Potential for Therapeutic Intervention in Non-Hodgkins Lymphoma	RP: B-cell lymphoma/leukemia 10 (BCL10) is a key mediator of the immune response. This study is to determine the function of nuclear BCL10 and its role in lymphomagenesis. MR: Military personnel are at greater risk for developing non-Hodgkin's lymphoma (NHL) because of exposure to cytotoxins and chemicals during deployment. The improvement in the prognosis and treatment options for NHL will benefit the military population.	*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				
CA140257 $545,497 Open	Bilgicer/ University of Notre Dame	Rational Engineering of Designer Nanoparticles to Target Multiple Myeloma	RP: To design and evaluate nanoparticles to target multiple myeloma (MM). MR: Exposure to chemicals such as Agent Orange increases the incidence rate of MM. This project could improve the therapeutic strategies for MM and benefit the military population at high risk for MM.	*New research – no outcomes reported to date*
CA140390 $561,600 Open	Reynaud/ Children's Hospital, Cincinnati	Investigating the Mechanisms of Leukemia Initiation in the Context of Obesity	RP: Obesity is a risk factor for leukemia, and is associated with an increased incidence rate and poor outcome. This study is to test the hypothesis that the alteration of the adipokine signals associated with obesity may promote leukemia; specifically, this study will focus on the role of adiponectin and leptin on normal and leukemia-initiating hematopoietic stem cells. MR: As obesity is prevalent in the Veteran population, the link between obesity and blood cancers constitutes a concern for military personnel and their families. This work will provide an understanding of the mechanism between obesity and cancer, which could benefit the military population in the long run.	*New research – no outcomes reported to date*
CA140437 $525,600 Open	Qin/ Louisiana State University Health Sciences Center	HGF/c-MET Pathway in AIDS-Related Lymphoma	RP: The hypothesis is that hepatocyte growth factor (HGF)/ c-MET pathway mediates primary effusion lymphoma (PEL) pathogenesis. The study intends to elucidate mechanisms for the HGF/c-MET pathway controlling PEL survival and growth, and to identify how viral oncogeneic proteins activate the HGF/ c-MET pathway. MR: Military personnel who served overseas may have high risk for exposure to HIV/KSHV infection and development of HIV/KSHV-related malignancies. PEL is a form of AIDS-related blood cancer.	*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				
CA140783 $576,001 Open	Qin/ City of Hope Beckman Research Institute	Development of Antibody Therapy against Immunosuppressive Cells in Blood Cancer Patients	RP: To identify novel human myeloid-derived suppressor cell (MDSC)-specific markers and to develop novel strategies to inhibit MDSCs and treat blood cancers. MR: This study will benefit both Veterans and active duty military members who face the potential for higher risk for blood cancers.	*New research – no outcomes reported to date*
CA140945 $612,000 Open	Ngo/ City of Hope Beckman Research Institute	The Role of Cyclin D1 in the Chemoresistance of Mantle Cell Lymphoma	RP: To define the mechanisms underlying chemoresistance of mantle cell lymphoma (MCL). The hypothesis is that cyclin D1 (CCND1) regulates checkpoint kinase 1 (CHEK1)-signaling to maintain cell survival and promote chemoresistance in TP53-deficient MCL by suppressing CCK5RAP3 expression. MR: Service members are at risk of developing blood cancers including lymphoma that may be caused by exposure to chemical and biological agents. This study will facilitate development of therapies for MCL and thus will have a positive impact on Service members.	*New research – no outcomes reported to date*
Cancers Related to Radiation Exposure				
CA140307 $475,995 Open	Chao/ Duke University	A Novel Therapeutic Target for Radiation-Induced Hematological Malignancies: Calcium Calmodulin Kinase 2	RP: Verify that STO-609, an inhibitor of the kinase CaMKK2, is a prototype of a new class of radiomitigator compounds that can prevent and cure radiation-induced blood cancer. This research has just been initiated. MR: Veterans who were exposed to radiation during military service have a higher risk of developing blood cancer as they age, and there are few drugs approved to mitigate the radiation injury.	*New research – no outcomes reported to date*

Log Number/ Amount/ Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Cancers Related to Radiation Exposure				
CA140822 $448,502 Open	Natarajan/ University of Texas Health Science Center at San Antonio	Protein Interaction in Tissue Microenvironment Initiates the Onset of Cancer in Response to Occupational and Environmental Radiation Exposure	RP: Investigate whether environmental or therapeutic radiation exposure alters the function of eNOS/NO signaling molecules to promote tumor initiation. MR: As Veterans or military personnel can have a higher risk for environmental or therapeutic radiation exposure, it is important to understand the mechanisms that drive tumor initiation and recurrence.	*New research – no outcomes reported to date*
Colorectal Cancer (CRC)				
CA110130 $364,800 POP Exp	Yue/ University of Notre Dame	Proteomic Analysis to Identify Functional Molecules in Drug Resistance Caused by E-Cadherin Knockdown in 3D-Cultured Colorectal Cancer Models	RP: A study that investigates whether CDH1, a gene encoding a cell-to-cell adhesion protein, drives the connection between drug resistance and metastasis using 3D cultures of CRC cells. Using this culture method, knockdown of CDH1 resulted in marked resistance to three out of four chemotherapeutic agents tested, thus supporting the claim that reduced CDH1 expression will help cancer cells acquire drug resistance. MR: CRC is the second leading cause of cancer death in the United States. This study could potentially lead to new targets for CRC treatment and reduce cancer burden among military beneficiaries.	*Publications: 2* *Presentations: 8*
CA120198 $374,403 POP Exp	Roper/ Tufts Medical Center	The Role of Akt Isoforms in Colorectal Cancer	RP: A study to determine the role of Akt, a protein known to influence cell growth and replication, in the malignancy of CRC. Results so far suggest that Akt isoforms are independently important for colorectal carcinogenesis and that Akt phosphorylation targets play an important role in colorectal cell growth and migration in vitro. MR: CRC is the second leading cause of cancer death in the United States. This study could potentially lead to new strategies for CRC treatment and reduce cancer burden among military beneficiaries.	*None to date*

Log Number/ Amount/ Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Colorectal Cancer (CRC)				
CA120296 $379,200 Open	Kizhakke Mattada/ University of Virginia	Functional Characterization of CENP-A Post-Translational Modifications in Chromosome Segregation	RP: A study to decipher the pathway that leads to epigenetic modification of CENP-A, and to determine the function it plays in chromosome segregation. Results suggest that CENP-A α-amino tri-methylation is a crucial post-translational modification in maintaining high fidelity of chromosome segregation and that any defect in this modification may result in aneuploidy and cancer. The research has shown that CENP-A is methylated by NRMT1 both in vitro and in vivo and occurs throughout the cell cycle. This methylation was found to contribute to cell survival with its absence resulting in senescence, a response stated to be dependent on the p53 pathway. MR: CRC is the second leading cause of cancer death in the United States. This study could potentially lead to new strategies for CRC treatment and reduce cancer burden among military beneficiaries.	*Presentations: 6*
CA120342 $417,600 Open	Sebastian/ Massachusetts General Hospital	Role of SIRT6 in Metabolic Reprogramming during Colorectal Carcinoma	RP: Aims to elucidate the role of the chromatin factor SIRT6 as a key regulator of glucose metabolism in the context of CRC. Results have demonstrated that SIRT6 acts as a potent tumor suppressor in CRC by controlling glucose metabolic programming, suggesting that targeting glycolysis may provide an approach to modulate cancer growth in tumors with low SIRT6 levels. Using two mouse models and an in vitro intestinal organoid system, the researchers found that a lack of SIRT6 increases the number and activity of intestinal stem cells, indicating that enhanced glycolytic metabolism in the absence of SIRT6 drives intestinal tumorigenesis via an increase of tumor initiating cells. MR: Understanding the metabolic reprogramming in CRC can offer an alternative way for therapeutic development and benefit military personnel impacted by CRC.	*Publications: 3* *Presentation: 1*

Log Number/ Amount/ Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Colorectal Cancer (CRC)				
CA120403 $373,200 Open	Shah/ University of Michigan, Ann Arbor	The Role of the Noncanonical NF-κB Pathway in Colon Cancer	RP: A study to determine the association of the NF-κB2 pathway and hypoxia in inflammation-associated CRC progression. Results suggest that NF-κB2 signaling does play an important role in modulating intestinal inflammation. Inhibition of this pathway led to a decreased number of cells that are responsible for immune tolerance in the intestine, suggesting that this pathway is a key player in dampening immune response and avoiding tissue damage due to aberrant inflammation. MR: Study results may lead to new targets for the development of therapeutics for CRC, which could benefit military personnel impacted by CRC.	*Presentation: 1*
CA130460 $388,800 Open	Lee/ Johns Hopkins University	Role of TRAIL Signaling through the Development of Carcinogen-Induced Colorectal Cancer	RP: To discover TRAIL family biomarkers that can serve to predict colitis-associated CRC risk by investigating the unexplored roles of TRAIL signaling across different stages of cancer development induced by chemical carcinogenesis. During the first year, mouse models were established to examine altered expression patterns of TRAIL-associated molecules, cytokines, and inflammatory markers at five disease stages, and clinical samples were analyzed to validate the functions of TRAIL-associated molecules in colon tissues from inflammatory bowel disease and colitis-associated colon cancer patients. MR: As Warfighters are at risk for exposure to environmental carcinogens associated with CRC development, the understanding and identifying of novel biomarkers at different stages of developing CRC will improve the success of preventive screening.	*Publication: 1* *Presentations: 2* *Patents: 3* *Funding obtained: 1 grant*

Log Number/ Amount/ Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Colorectal Cancer (CRC)				
CA130575 $543,815 Open	Rauscher/ Wistar Institute	Control of Colon Cancer Progression by the Colon Microbiome	RP: To test whether NLEE, a bacterially encoded virulence effector protein, induces genomic instability and contributes to the development of CRC. Initial research into the crystal structure of NLEE revealed a unique methylated DNA binding configuration and computational docking experiments illustrated the mechanism of NLEE binding site recognition. MR: Military personnel can be exposed to noxious pathogens that invade the gut and have long-term influences on CRC development and progression.	*Publication: 1* *Presentation: 1*
CA140515 $461,399 Open	Ellis/ University of Texas MD Anderson Cancer Center	Unbiased Screening for Identification of Effective Combination Therapies Targeting Oncogenic Pathways in Colorectal Cancer	RP: This study aims to develop a screen to test combinatorial therapies against CRC cells and assess the efficacy of these new drug combinations against patient-derived xenografts. MR: CRC is the second leading cause of cancer death in the United States. This study could potentially lead to new strategies for CRC treatment and reduce cancer burden among military beneficiaries.	*New research – no outcomes reported to date*
CA140572 $576,000 Open	Park/ University of Texas MD Anderson Cancer Center	Dissecting TMEM9, a Wnt Signaling Regulator of Colorectal Cancer	RP: Study to determine the role of TMEM9 in intestinal tumorigenesis using mouse models and evaluate cancer drugs in their ability to target TMEM9-regulated WNT signaling. This research has just been initiated. MR: Veterans are a high-risk population for exposure to agents known to be associated with human cancers, including CRC. Novel therapeutics for CRC, one of the most deadly among all cancers, may improve health outcomes for this population.	*New research – no outcomes reported to date*

Log Number/ Amount/ Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Colorectal Cancer (CRC)				
CA140577 $310,000 Open	Gorham/ Naval Health Research Center	Serum 25-Hydroxyvitamin D and Subsequent Incidence of Colorectal Cancer in Active-Duty Personnel: A Nested Case-Control Study	RP: To quantify the relationship between 25-hydroxyvitamin D (25(OH)D) serum levels and incidence of CRC in active duty personnel. MR: This study will quantify prospectively the relationship between 25(OH)D levels in sera and CRC risk in active duty military, and provide information to indicate whether vitamin D may be useful in primary prevention of CRC.	*New research – no outcomes reported to date*
CA140616 $490,546 Open	Burnett-Hartman/ Kaiser Foundation Research Institute	The Association between Molecular Markers in Colorectal Sessile Serrated Polyps and Colorectal Cancer Risk	RP: A study to determine if there is a correlation between the histological characteristics of sessile serrated polyps (SSPs) and CRC risk in patients. MR: SSPs are associated with cigarette smoking, and cigarette smoking is associated with various cancers. Given that the prevalence of cigarette use in the military population is higher than the general population, the utilization of SSPs as a new marker of CRC risk may benefit the military population.	*New research – no outcomes reported to date*
CA140772 $466,500 Open	Arcaroli/ University of Colorado at Denver	Targeting the ALDH+ Tumorigenic Population in Colorectal Cancer	RP: This study will assess the effect of novel compound combinations that target WNT- and NOTCH-signaling pathways on tumor progression using patient-derived cells. Promising combinations will then be validated against patient-derived xenografts. MR: CRC is the second leading cause of cancer death in the United States. This study could potentially lead to new strategies for CRC treatment and reduce cancer burden among military beneficiaries.	*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)				
CA140816 $538,480 Open	Levi/ Wake Forest University Health Sciences	Fluorescent Electrically Conductive Nanoparticles for Detection and Treatment of Metastatic Colorectal Cancer	RP: Develop CRC-targeted nanoparticles for photothermal ablation and demonstrate their efficacy in targeting chemotherapy-resistant cancer cells in a mouse model. MR: CRC is the second leading cause of cancer death in the United States. This study could potentially lead to new strategies for CRC treatment and reduce cancer burden among military beneficiaries.	*New research – no outcomes reported to date*
CA140882 $466,500 Open	Dakshanamurthy/ Georgetown University	Novel High-Fidelity Screening of Environmental Chemicals and Carcinogens and Mechanisms in Colorectal Cancer	RP: Identify the molecular targets and potential toxicity of environmental chemicals through *in silico* protein-chemical interaction mapping and intrinsic chemical properties modeling. Biochemical validation and characterization of protein-chemical interaction will also be performed. MR: Environmental chemical exposure may be an unavoidable risk of deployment and other operations. A better understanding of the molecular targets and toxicity of these environmental toxicants will help to determine the relative cancer risk posed to military personnel and their families.	*New research – no outcomes reported to date*
CA140948 $448,500 Open	Curiel/ University of Texas Health Science Center at San Antonio	Novel Listeria Vectors Secreting Gut Flora-Altering Agents to Prevent Colon Cancer and Treat Colitis	RP: Aims to modify the levels of B7-H1 expression within the gut using listeria as the modifying agent, and determine the connection between B7-H1-mediated changes in the gut and reduced CRC risk. MR: Colon inflammation increases one's risk of CRC. More than 35,000 cases of inflammatory bowel disease were identified in Military Health System beneficiaries within a single year. The development of methods to promote gut health may help mitigate the contribution of colitis to CRC risk.	*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)				
CA150370/P1/P2 $1,735,601 Under Neg	Yeung; Pillarisetty/ University of Washington Tian/ Institute for Systems Biology	Tumor Slice Culture: A New Avatar in Personalized Oncology	RP: To establish a platform to interrogate drug sensitivity and to correlate the results with clinical and molecular data. Cytotoxic chemotherapy, targeted kinase inhibitors, and immunotherapy will be tested on patient-derived tumor slice cultures of CRC liver metastases. MR: Military Service members are exposed to various chemicals, biologics, and environmental toxicants distinct from civilians, which may result in cancer that exhibit distinctive biology or response to treatment. A personalized approach to treatment selection is therefore highly desirable.	*Research not yet initiated*
CA150494 $534,985 Under Neg	Wei/ University of Kentucky	Targeting Sulfiredoxin in Colorectal Cancer	RP: Understand the mechanisms by which Sulfiredoxin (Srx), a protein that contributes to oxidative stress resistance, activates oncogenic signaling to promote CRC cell malignancy. Cell culture experiments as well as mouse xenograft models will be used to interrogate the functional role of Srx in CRC development. MR: CRC is the second leading cause of cancer death in the United States. This study could potentially lead to new strategies for CRC treatment and reduce cancer burden among military beneficiaries.	*Research not yet initiated*

Log Number/ Amount/ Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Colorectal Cancer (CRC)				
CA150582 $607,999 Under Neg	Moriarity/ University of Minnesota Twin Cities	Targeted Therapy Combined with Immune Modulation Using Gold Nanoparticles for Treating Metastatic Colorectal Cancer	RP: Generate gold nanoparticles (AuNPs) for the targeted delivery of a combinatorial therapy of immunogenic peptides and oncogene inhibitors. The utility of the AuNPs will be assessed in vivo for a mouse model of CRC. MR: CRC is the second leading cause of cancer death in the United States. This study could potentially lead to new strategies for CRC treatment and reduce cancer burden among military beneficiaries.	*Research not yet initiated*
CA150595 $569,636 Under Neg	Viswanath/ Case Western Reserve University	MRI-Pathology Correlation for Image Analytics-Based Treatment Outcome Assessment and Margin Planning in Rectal Cancers	RP: To develop novel computerized tools that utilize post-treatment MRI data to provide clinically actionable information about surgical treatment and its predicted benefit. Two new tools for CRC post-treatment assessment will be developed and validated against patient data from university hospitals as well as the Cleveland VA Medical Center. MR: CRC is the second leading cause of cancer death in the United States. This study could potentially lead to new strategies for CRC treatment and reduce cancer burden among military beneficiaries.	*Research not yet initiated*

Log Number/ Amount/ Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Colorectal Cancer (CRC)				
CA150731 $130,751 Under Neg	Gokare/ Institute for Cancer Research	Modulation of Therapeutic Response and Pharmacokinetics of 5-FU by P53 through Repression of the Pyrimidine Catabolic Gene Dihydropyrimidine Dehydrogenase (DPYD)	RP: A study to assess the role of p53 mutations in the alteration of metabolism and therapeutic sensitivity of 5-Fluorouracil (5-FU), the major component of CRC chemotherapy. Will use a combination of cancer cell lines and transgenic mice with known mutations in the p53 tumor suppressor gene and assess expression level difference of 5-FU metabolic protein, DPYD, as well as cell proliferation and viability in the presence of the chemotherapeutic agent. MR: CRC is the second leading cause of cancer death in the United States. This study could potentially lead to new strategies for CRC treatment and reduce cancer burden among military beneficiaries.	*Research not yet initiated*
CA150808 $125,250 Under Neg	Tosti/ Albert Einstein College of Medicine	The Role of Mismatch Repair and Microbiome in Inflammation-Associated Colon Cancer	RP: A study to investigate the relationship between TGFBRII inactivation and the colonic microbiota in DNA mismatch repair (MMR)-driven tumorigenesis. This study will investigate the differences in survival, tumor incidence/location, and histopathology of MMR-impaired mice and examine the impact on colon tumorigenesis upon intestinal microbiota alteration. MR: CRC is the second leading cause of cancer death in the United States. This study could potentially lead to new strategies for CRC treatment and reduce cancer burden among military beneficiaries.	*Research not yet initiated*

Log Number/ Amount/ Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Colorectal Cancer (CRC)				
CA150873 $127,125 Under Neg	Sauer/ New York University School of Medicine	Structure and Function of the Reduced Folate Carrier	RP: A project to solve the 3D crystal structure of the human Reduced Folate Carrier (hRFC) protein. Folates play an important role in cellular metabolism and limitations in cellular folate levels or defects in the folate cycle have been linked to cancer risk. This project will provide fundamental information about the structure of hRFC and a basis for future rational drug design. MR: A structural description of hRFC is necessary for structure-based drug design of novel chemotherapeutics acting on the folate pathway. This work will directly benefit Service members, their families, and beneficiaries by accelerating the development of new chemotherapies.	*Research not yet initiated*
CA150899 $113,625 Under Neg	Carpenter/ St. Louis University	Colorectal Cancer Immunotherapy by Pharmacological Suppression of Liver X Receptor Activity	RP: To investigate the role of liver X receptor (LXR) activation in the process of immune evasion by tumor cells. The study will determine whether blocking the receptor/ligand interaction of activating signals released by tumors is sufficient to stimulate T-cell response to CRC cells in vitro. Additional experiments will test the efficiency of these blocking agents to treat CRC in mice. MR: CRC is the second leading cause of cancer death in the United States. This study could potentially lead to new strategies for CRC treatment and reduce cancer burden among military beneficiaries.	*Research not yet initiated*

Log Number/ Amount/ Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Colorectal Cancer (CRC)				
CA150908 $108,000 Open	Gomez/ University of Kansas Center for Research, Inc.	A Role for APC in Goblet Cell Function and the Unfolded Protein Response	RP: To determine the regulation, role, and function of the tumor suppressor Adenomatous Polyposis Coli (APC) in unfolded protein response (UPR) in CRC cell lines. Will also investigate the effect of chemical stimulation of UPR on APC levels and inflammation using mice with induced colitis. MR: Approximately 10%-15% of inflammatory bowel disease patients die from CRC. CRC is the second leading cause of cancer death in the United States. This study could potentially lead to new strategies for CRC treatment and reduce cancer burden among military beneficiaries.	*Research not yet initiated*
Genetic Cancer				
CA100865/P1/P2 $1,085,960 Open	Alvarez; Couto; Huang/ Research Institute at Nationwide Children's Hospital; Ohio State University	Integrative Lifecourse and Genetic Analysis of Military Working Dogs	RP: Identification of environmental influences with potential to alter gene structure, stability, and expression, thereby altering cancer risk. Identification of specific genetic variations and environmental exposures, resulting in different epigenetic profiles capable of modifying cancer risk. The informatics infrastructure, statistical method for analyzing genetic data, and military dog registry database are established. Collection of blood samples and health records for the military working dogs has been initiated and analysis is in progress. MR: The study of military working dogs, environmental exposures, and cancer risk will directly relate to military exposures and cancer risk within the human handlers population.	*Publications: 3* *Presentations: 7*

Log Number/ Amount/ Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Genetic Cancer				
CA140196 $446,542 Open	Walkley/ St. Vincent's Institute of Medical Research	How Does a DNA Helicase Regulate Blood Cell Development and Disease?	RP: Understand the role of the DNA helicase, RECQL4, in regulating hematopoiesis and the development of blood cancer. DNA helicases are involved in many cellular processes, including DNA repair. MR: The military population may be at high risk for exposure to DNA-damaging agents or carcinogenic chemicals. Thus, it is important to understand how these agents may lead to disease.	*New research – no outcomes reported to date*
CA140303 $569,841 Open	Moldovan/ Pennsylvania State University	The PCNA-PARI Pathway of Genome Stability in Cancer	RP: Test the hypothesis that the protein PCNA-associated recombination inhibitor (PARI) promotes leukemia by blocking DNA damage-induced differentiation. MR: Radiation exposure is a well-known, militarily relevant risk factor for cancer. Radiation creates DNA damage; in particular, radiation exposure results in increased incidence of leukemia. This research investigates a new pathway that repairs radiation-induced DNA damage and explores its impact on leukemia development and treatment.	*New research – no outcomes reported to date*
CA140321 $528,000 Open	MacPherson/ Fred Hutchinson Cancer Research Center	Developing a KMT2D/MLL2-Deleted Preclinical Mouse Model of Bladder Urothelial Cancer	RP: Develop a mouse model of bladder cancer that exhibits several bladder cancer markers, and test a new hypothesis for treating bladder cancer. MR: Smoking is a known risk factor for bladder cancer. Use of tobacco products occurs at higher rates in active duty military population than the general population. This work has potential to benefit military personnel and their families impacted by bladder cancer.	*New research – no outcomes reported to date*

Log Number/ Amount/ Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Genetic Cancer				
CA150188 $708,000 Under Neg	Cantor/ Children's Hospital Boston	Genetic Risk Factors for Clonal Hematopoiesis and Leukemia Development Following Ionizing Radiation and Chemical Exposure	RP: To determine if pre-existing genetic mutations within members of the DNA damage response (DDR) pathway lead to a selective advantage for cells within the bone marrow that are predisposed to genomic instability upon exposure to low-level ionizing radiation. Mice deficient in specific DDR members will be used to evaluate this effect in vivo. MR: This research is directly relevant to members of the Armed Forces and their families who may have increased risk of exposure to ionizing radiation and DNA-damaging chemicals.	*Research not yet initiated*
CA150414 $606,975 Under Neg	Magnuson/ University of North Carolina at Chapel Hill	Co-Occurrent Mutations in Chromatin Regulators Define Genetically Distinct Forms of Cancer	RP: To create a pipeline to prioritize mutations commonly found in hepatocellular carcinoma, characterize their effect on tumorigenesis in vitro and in vivo, and identify genes that are synthetically lethal in mouse models. Linking data on co-occurring somatic mutation rates with new genome-editing techniques will allow for analysis of many more combinations of mutations that have not been evaluated in the past. 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 between 1945 and 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.	*Research not yet initiated*

Log Number/ Amount/ Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Genetic Cancer				
CA150506 $556,116 Under Neg	Meeks/ Northwestern University	The Role of EZH2 in High-Risk Nonmuscle Invasive Bladder Cancer	RP: To test the hypothesis that Enhancer of Zeste-2 (EZH2), a histone methyltransferase, is overexpressed in invasive bladder cancer resulting in global changes in histone methylation, which creates a cellular shift toward epithelial to mesenchymal transition, increasing expression of development genes and repressing genes involved in cellular matrix and intracellular junctions. This study will also determine the role of EZH2 in bladder cancer using a murine model of bladder cancer. Patient samples collected from both civilian and VA populations will be used to try to identify biomarkers of high-risk non-muscle invasive bladder cancer. MR: This research addresses military-relevant risk factors (i.e., environmental carcinogens) and gaps in bladder cancer risk prediction, detection, and treatment for military members and Veterans.	*Research not yet initiated*
CA150794 $127,125 Under Neg	Daniloski/ New York University School of Medicine	Elucidate the Mechanism of Telomere Maintenance in STAG2 Mutated Tumor Cells	RP: To test the hypothesis that STAG2-mutated tumors utilize both telomerase and ALT to elongate their telomeres and that forced resolution of the persistent telomere cohesion will lead to rapid cancer cell death. MR: Due to exposure to ionizing radiation, chemicals, and environmental carcinogens, military personnel are at particularly high risk for DNA damage that can lead to increased gene mutations and promote cancer formation. This study addresses how tumors carrying mutations in STAG2 gene maintain their telomeres.	*Research not yet initiated*

Log Number/ Amount/ Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Genetic Cancer				
CA150795 $131,925 Under Neg	Ghisays/ Memorial Sloan Kettering Cancer Center	RTEL1 and Genome Stability	RP: To examine the functions of RTEL1 in cells and in a mouse model to better understand the role of genome stability in the development and aging of proliferative tissues and tumor suppression. MR: While cancer, including myeloid proliferative disorders, affects Service members, their families, and the general population, a complete understanding of initiation and progression of cancer remains unknown. The characterization of RTEL1 biology in the context of the myeloid proliferative disorders and cancer development will provide unique insights that may be immediately translated into clinical care.	*Research not yet initiated*
CA150827 $108,350 Under Neg	Roberts/ Northwestern University	Cobalt(III) Schiff Base Complexes as Inhibitors of p53 Aggregation in Cancer	RP: Recent research indicates that aggregation of mutant p53 leads to a dominant negative effect on any wild-type p53 that may be remaining in tumor cells. The PI proposes to design and synthesize Cobalt (III) Schiff Bases that target mutant p53 and prevent aggregation. MR: Mutations in p53 are the most common clinically observed cancer causing mutations and present in over 50% of all cancers. The development of a novel therapeutic would benefit Service members, Veterans, and military beneficiaries who are affected by cancers containing p53 mutations.	*Research not yet initiated*

Log Number/ Amount/ Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Genetic Cancer				
CA150844 $81,000 Under Neg	Wadugu/ Washington University	The Role of Mutant U2Af1 in the Pathogenesis of Myelodysplastic Syndromes	RP: The PI will create a novel mouse model of myelodysplastic syndrome (MDS) to determine if and how two mutations that often co-occur in the same tumor, U2AF1 and ASXL1, lead to tumorigenesis. MR: Identifying genetic mutations contributing to MDS initiation is key to developing effective prognostic and therapeutic strategies. The mouse models created here will be valuable resources for the research community to test drugs in future research.	*Research not yet initiated*
CA150882 $125,694 Open	Hsieh/ Cornell University Weill Medical College	Characterization of Ran Binding Protein (RANBP6) as Candidate Tumor Suppressor	RP: To test the hypothesis that the tumor suppressor function of Ran-binding protein 6 (RanBP6) stems from its role as regulator of nuclear import/export. The PI will identify RanBP6 substrates, characterize RanBP6 mutations that are common in multiple types of cancer, and explore the tumor suppressor activity of RanBP6 in a murine pancreatic organoid model. MR: These studies aim to broaden the currently rudimentary knowledge on how Ran and Ran-binding proteins contribute to tumorigenesis and will provide new opportunities to therapeutically target deregulated growth factor signaling in cancer, and benefit Service members, Veterans, and their families who may have an increased risk of developing cancer due to a higher chance of exposure to carcinogens.	*New research – no outcomes reported to date*

Log Number/ Amount/ Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Kidney Cancer				
CA100606/P1 $1,206,215 Open	Tewari/ Fred Hutchinson Cancer Research Center Pantuck/ University of California, Los Angeles	Early Diagnosis of Clear Cell Kidney Cancer via VHL/HIF Pathway-Regulated Circulating microRNA	RP: Development of a serum miRNA-based biomarker for early detection of kidney cancer. Initially optimized the detection method for miR-210. Demonstrated that miR-210 was elevated in renal carcinoma serum samples. Identified seven additional miRNAs as potential serum biomarkers, which will be further examined along with miR-210. MR: Successful development of such a test will enable early kidney cancer detection, removal at a curative and kidney-sparing stage, prompt recovery, and contribute toward improved readiness.	*Publication: 1*
CA120297 $364,353 Open	Krishnan/ University of North Carolina at Chapel Hill	Reprogramming of the Kinome to Enhance Mammalian Target of Rapamycin (mTOR) Inhibitor Responsiveness in Renal Cell Carcinoma	RP: To identify kinases upregulated by mammalian target of rapamycin (mTOR) inhibitors in renal cancer cells and determine if downregulation of these kinases improves the responsiveness of renal cancer cells to mTOR inhibitors. To date, the PI has found that the combination therapy of Dasatinib/Everolimus overcomes the acquired resistance to Everolimus alone in a PDX model of renal cell carcinoma (RCC). The combination prolongs survival and reduces tumor burden in mice. MR: This study could potentially improve the outcomes and survival of military personnel with RCC.	*Publication: 1* *Presentation: 1*
CA130028 $474,562 Open	Czyzyk-Krzeska/ University of Cincinnati	Effects of Tobacco Smoke (TS) on Growth of Clear Cell Renal Cell Carcinoma (ccRCC)	RP: To identify somatic mutations in DNA extracted from clear cell renal cell carcinoma (ccRCC) tumors from male Veterans who were heavy smokers as compared to matched ccRCC patient non-smokers and identify gene expression profiles. The PI is currently collecting the necessary number of tumor samples before beginning the analysis in order to minimize technical errors. MR: There is a high prevalence of smoking in male active military personnel and Veterans along with a higher rate of kidney cancer than the general population.	*None to date*

Log Number/ Amount/ Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Kidney Cancer				
CA130458 $602,996 Open	Ebos/ Health Research Inc., Roswell Park Division	Distinguishing Tumor- and Stromal-Mediated Mechanisms of Resistance and Rebound in Models of Metastatic Renal Cell Carcinoma	RP: Investigate the role of tumor and stromal reactions to antiangiogenic therapy in RCC mouse models. To date, the PI has optimized the amount of time between neoadjuvant treatment and surgery to remove tumors, and he is working on developing a descriptive scale to stratify/distinguish between treatment effects as either against the primary tumor site, metastatic site(s), or both, after tumor removal. MR: Service members have higher risk to develop kidney cancer because of deployment-related exposure to environment hazards.	*Publication: 1 review* *Presentations: 7*
CA140443 $547,200 Open	Zhang/ University of North Carolina at Chapel Hill	Validation of ZHX2 as a Novel pVHL E3 Ligase Substrate and Its Role in Kidney Cancer	RP: Confirm that zinc finger homeobox protein 2 (ZHX2) levels are negatively regulated by the tumor suppressor pVHL, and determine the functional relevance of ZHX2 in renal cell carcinogenesis. MR: The proposed work can have potentially significant impact on military beneficiaries because (1) smoking cigarettes, which 30% of active duty personnel do, is a significant risk factor for RCC and (2) occupational exposure to heavy metals, paints, organic solvents, and other combat-related chemicals significantly increases the risk of RCC.	*New research – no outcomes reported to date*

Log Number/ Amount/ Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Kidney Cancer				
CA140497 $585,000 Open	Sabatini/ Whitehead Institute for Biomedical Research	Role of Lysosomal Transporters in Promoting the Growth of Clear Cell Renal Cell Carcinoma and Other Tumor Types	RP: Develop and LC/MS protocol to rapidly isolate epitope-tagged lysosomes. Using this protocol, identify lysosomal transporters that are overexpressed or deleted in ccRCC and determine their cellular functions. MR: The leading risk factors for ccRCC are smoking, hypertension, and chronic kidney dialysis, all of which are more prevalent among military beneficiaries than in the general population. The proposed research will provide the basis for developing new anti-cancer drugs to improve therapeutic options and decrease the burden of ccRCC on the military health care system.	*New research – no outcomes reported to date*
CA140917 $486,000 Open	Hammers/ Johns Hopkins University	Enhancing Immune Checkpoint Inhibitor Therapy in Kidney Cancer	RP: Test the hypothesis that patient responses to immune checkpoint inhibitors will be improved by auto-vaccination approaches, and that these approaches will synergize with other immune-targeting therapies. MR: Service members have higher risk to develop kidney cancer because of deployment-related exposure to environment hazards.	*New research – no outcomes reported to date*

Log Number/ Amount/ Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Kidney Cancer				
CA150289 $780,000 Under Neg	Rastinejad/ Sanford-Burnham Medical Research Institute, Orlando	Novel Hypoxia-Directed Cancer Therapeutics	RP: Test the hypothesis that the ligand binding pockets of HIF-1α/ARNT and HIF-2α/ARNT can be targeted for drug discovery through small molecule inhibitors. The short-term objectives are to identify diverse novel small molecule inhibitors for each of HIF-1α and HIF-2α proteins using high-throughput screening and cell culture functional characterization. The long-term goals are to evaluate the most promising compounds through synthetic medicinal chemistry, pharmacology, and animal studies. MR: HIF-targeted drugs can broadly impact both civilian and military personnel suffering from advanced cancers. The new treatment options that may ultimately emerge from this research would benefit patients with a variety of cancers that are currently resistant to existing treatments.	*Research not yet initiated*
CA150395 $569,236 Under Neg	Leppert/ Stanford University	IQGAP1 Scaffold-Kinase Interaction Blockade in Renal Cell Carcinoma: A Novel Biomarker and Therapeutic Strategy	RP: The intracellular scaffold protein IQGAP1 is required for ERK1/2-driven tumor progression. The PI will evaluate IQGAP1 expression in RCC clinical samples, and correlate this to RAS signaling, the signaling pathway that involve ERK1/2, and clinical outcomes. Additionally, the PI will study IQGAP1 inhibitors in tissue slice cultures and patient-derived xenograft models. MR: RCC is the fourth most common solid tumor diagnosed among military beneficiaries receiving care in the VA healthcare system.	*Research not yet initiated*

Log Number/ Amount/ Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Liver Cancer				
CA150178 $610,200 Under Neg	Lujambio/ Icahn School of Medicine at Mount Sinai	Functional Genomics Screen for Combination Therapy Discovery in Liver Cancer	RP: A study to develop new combinatorial therapies for hepatocellular carcinoma that increase the efficacy of palbaciclib, a Food and Drug Administration (FDA)-approved cancer treatment. Work will use a molecular knockdown approach to identify genes and pathways that regulate palbaciclib activity. MR: The incidence of hepatocellular carcinoma (HCC) is increasing in the U.S., especially within the military and Veterans populations. Main risk factors for HCC, such as alcohol consumption, hepatitis B and C infection, obesity, and male gender, are over-represented within the military and Veterans populations.	*Research not yet initiated*
CA150245/P1/ P2/P3/P4 $1,818,164 Under Neg	Zhu; Yopp; Singal; Siegwart/ University of Texas Southwestern Medical Center at Dallas Waljee/ University of Michigan	Defining Hepatocellular Carcinoma Subtypes and Treatment Responses in Patient-Derived Tumorgrafts	RP: A study to better understand the basic biology of HCC at different disease stages. Using patient-derived xenografts, the molecular signature of HCCs will be established, and their susceptibility to small RNA therapies will be investigated. The patient-derived xenografts will also be examined to identify predictive biomarkers for small molecule sensitivity. MR: The military population is particularly vulnerable to HCC, given higher rates of hepatitis C virus (HCV) infection, obesity, diabetes, and alcohol abuse than the general population. Over the last 10 years, HCC incidence has more than tripled among Veterans.	*Research not yet initiated*

Log Number/ Amount/ Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Liver Cancer				
CA150248 $613,200 Under Neg	Lau/ Northern California Institute for Research and Education	The Genetic Basis of Sex Differences in Liver Cancer	RP: To validate a male-specific cancer gene, TSPY, as a diagnostic and predictive marker in HCC. Will establish the contribution of TSPY and other Y chromosome-expressed genes to HCC pathology. MR: Risk factors pertaining to HCC are most prevalent among military members and Veterans. The proposed research plans to validate TSPY as a diagnostic and predictive marker of HCC utilizing patients from the VA Hospital in San Francisco.	*Research not yet initiated*
CA150262 $438,152 Under Neg	Albrecht/ VA Medical Center Minneapolis, MN	The Role of CDK2 in Hepatocellular Carcinoma	RP: Explore the mechanisms by which the cell cycle regulator, cdk2, contributes to HCC. Using a mouse model that is highly protected against HCC development, genes contributing to cdk2 pathology will be identified. MR: The proposed research is highly relevant to Veterans because of the increasing incidence of HCC in this population.	*Research not yet initiated*
CA150272/P1/ P2/P3/P4 $2,047,765 Under Neg	Friedman; Llovet; Lujambo; Villanueva/ Icahn School of Medicine at Mount Sinai Lowe/ Memorial Sloan Kettering Cancer Center	Mechanisms of Acquired Resistance to Sorafenib in Hepatocellular Carcinoma	RP: Identify the critical elements of sorafenib resistance in HCC. Using a combination of patient-derived biopsies, 3D cultured organoids, and tumor stroma samples, the molecular mechanism of therapeutic resistance will be investigated and second line drug targets will be identified and validated. MR: The incidence of HCC is increasing in the U.S., especially within the military and Veterans populations. Among the main risk factors for HCC development are alcohol consumption, hepatitis B and C infection, obesity, and male gender, all of which are over-represented in the military and Veterans populations.	*Research not yet initiated*

Log Number/ Amount/ Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Liver Cancer				
CA150281 $664,359 Under Neg	Hoshida/ Icahn School of Medicine at Mount Sinai	Gene Regulatory Networks as Targets and Biomarkers for Liver Cancer Chemoprevention after Clearance of Oncogenic Hepatitis C Virus	RP: To develop an experimental system that will enable identification of cancer prevention targets and biomarkers of HCC post-HCV clearance. A cell-based model will be used to describe molecular changes that occur as a result of oncogenic HCV. MR: The prevalence of HCV infection in Veterans is more than three-fold higher than in the general population. The number of Veterans with HCV-related HCC has increased nine-fold over the past decade.	*Research not yet initiated*
CA150480 $677,998 Under Neg	Yu/ Icahn School of Medicine at Mount Sinai	Enhancing Efficacy of the PD-1/PD-L1 Inhibitor-Mediated Anti-Liver Cancer Immunotherapy through Promoting CD8+ T-Cell Infiltration by Targeting Angiopoietin-1	RP: Aims to develop a novel way to enhance therapeutic efficacy of FDA-approved immune checkpoint inhibitors against HCC. Will examine whether inhibition of Angpt1, a potential target of established oncogenes, will contribute to enhanced tumor clearance in mouse models of HCC. MR: Rates of HCC are on the rise in Western countries largely due to obesity and HCV infection as there is no vaccine against HCV. Military personnel have an increased chance of HCV infection during deployment and combat and are at higher risk of developing HCC.	*Research not yet initiated*

Log Number/ Amount/ Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Liver Cancer				
CA150590/P1/ P2/P3/P4 $1,977,778 Under Neg	Schook/ University of Illinois at Urbana-Champaign Solomon; Brown; Boas/ Memorial Sloan Kettering Cancer Center Gaba/ University of Illinois at Chicago	Genetically Inducible Porcine Model of Primary and Metastatic HCC in Comorbidity Host Environments for Interventional Radiology-Guided Detection and Treatment	RP: To develop a porcine model of HCC. Porcine HCC will be characterized in comparison to the human disease to determine the utility of the model system for disease progression, tumor host environmental effects, and disease treatment strategies. MR: HCC is exceedingly common in the Veteran population due to a high incidence of alcoholic cirrhosis and viral hepatitis.	*Research not yet initiated*
CA150690 $115,500 Under Neg	Xu/ University of California, Los Angeles	Development of a Synthetic Lethal Drug Combination that Targets the Energy Generation Triangle for Liver Cancer Therapy	RP: To examine the combinatorial effect of inhibiting multiple energy production pathways specific to HCC. By targeting the three main pathways of energy production, the researchers will investigate whether this strategy facilitates tumor clearance unlike single target therapy, which only slows or stops tumor growth without reducing tumor size. MR: Despite the increasing prevalence and lethality of HCC in the U.S. and among Veterans, there is a lack of effective and safe drugs available for clinical treatment.	*Research not yet initiated*

Log Number/ Amount/ Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Liver Cancer				
CA150850 $130,500 Under Neg	Liu/ Massachusetts General Hospital	Molecular Characterization of FGFR2 Fusions in Cholangiocarcinoma	RP: To understand the role of fibroblast growth factor receptor 2 (FGFR2) genomic translocations in the pathogenesis of a specific form of bile duct cancer, intrahepatic cholangiocarcinoma (ICC). A new mouse model of ICC will be engineered and small molecule inhibitors of FGFR signaling will be tested for efficacy against patient-derived xenografts. MR: For unknown reasons, more and more people are being diagnosed with ICC, which affects the bile ducts of the liver. Patients typically die within 1 year of diagnosis, and treatment with chemotherapy has limited effectiveness. The risk factors for ICC are similar to those of other chronic liver diseases, and include chronic alcohol consumption, obesity, and viral hepatitis, all of which affect military personnel and Veterans.	*Research not yet initiated*
CA150866 $109,480 Under Neg	Tackmann/ University of North Carolina at Chapel Hill	Characterizing the Role of Hep27 in Liver and Colorectal Cancer Stress Tolerance	RP: To investigate the role of Hep27 in conferring resistance to oxidative stress within cancer cells by increasing reactive oxygen species (ROS) tolerance. Using liver and colorectal cancer cell lines, this research will examine the molecular mechanism of ROS tolerance within Hep27-expressing cells and determine if Hep27 expression is a modulator of therapeutic sensitivity. MR: The military population is particularly vulnerable to HCC given the higher rates of behavioral and environmental risk factors including HCV infection, obesity, diabetes, and alcohol abuse.	*Research not yet initiated*

Log Number/ Amount/ Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Melanoma/Skin Cancer				
CA093370/P2 $1,188,381 Open	Kashani-Sabet; Leachman/ California Pacific Medical Center; University of Utah	Molecular Determinants of Melanoma Susceptibility and Progression	RP: Development of a melanoma risk prediction model in the military population. Completed preparation for sample analysis. Obtained permission to access the Department of Defense Automated Central Tumor Registry database. Submitted the query to the database. Sample analysis is in progress. MR: Deployment to areas of high UV exposures puts Service members at increased risk for the development of melanoma and other skin cancers. Study directly relates to military population and risk.	*None to date*
CA110094 $322,849 POP Exp	Callahan/ Memorial Sloan Kettering Cancer Center	Evaluation of the Immunologic Impact of RAF Inhibitors to Guide Optimal Combination of RAF Inhibitors and Immunotherapy for the Treatment of Advanced Melanoma	RP: Findings suggest a model where RAF inhibitors are likely to combine with immunotherapies to generate robust, long-lasting anti-tumor T-cell responses while MEK inhibitors may compromise the generation of long-lasting T-cell memory. Data support a superior anti-tumor effect in vivo with BRAFi+CTLA-4 blockade or BRAFi+ PD-1 blockade versus monotherapy. MR: Service members are deployed to areas of high risk for exposure to UV light.	*Publication: 1* *Presentations: 3* *Funding obtained: 1 grant* *Employment: The PI was appointed to a faculty position*
CA120099 $400,800 Open	Ceol/ University of Massachusetts Medical School	Uncovering the Role of BMP Signaling in Melanocyte Development and Melanoma Tumorigenesis	RP: Investigation of the bone morphogenetic protein GDF6 in melanocyte development and melanoma tumorigenesis. Results support that GDF6 promotes melanoma initiation and maintenance and knockdown of the gene impairs melanoma growth. MR: Melanoma is one of the most common cancers among active duty personnel. Study results may lead to a diagnostic and prognostic marker of melanoma.	*Publications: 2* *Presentations: 4*

Log Number/ Amount/ Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Melanoma/Skin Cancer				
CA130184 $585,000 Open	Ronai/ Sanford-Burnham Medical Research Institute	Siah1/2 Ubiquitin Ligases in ER Stress Signaling in Melanoma	RP: To determine the significance of the Siah2-hypoxia-ER stress regulatory axis in melanoma development and progression and to evaluate the use of Siah1/2 and ER stress inhibitors as potential therapeutics. Developed a first-in-class inhibitor for ubiquitin ligases which inhibit "cancer-like" phenotypes within cultured cells. MR: The risk for melanoma development is significantly higher in a younger age group (16-25), making the development of new treatments and preventions of melanoma pertinent for active Service members.	*Publication: 1* *Presentations: 3* *Patent: 1*
CA130316 $450,520 Open	Setaluri/ University of Wisconsin–Madison	Noncoding RNA Network in Cutaneous Melanocytes: Regulation by UV and Role in Melanomagenesis	RP: To understand the mechanisms by which UV-induced molecular changes contribute to cutaneous melanoma development to identify tissue biomarkers. Identified candidate miRNAs that are regulated in melanocytes and melanoma cells. Further work will characterize the UV-induced changes of these miRNAs and their effect on melanocyte transformation. MR: Identification of new molecular markers that are regulated by UV will greatly improve the risk assessment of active duty military personnel deployed to sun-intense locations.	*Presentation: 1*

Log Number/ Amount/ Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Melanoma/Skin Cancer				
CA130351 $550,800 Open	Wang/ Medical College of Wisconsin	Novel Combinatorial Immunotherapy for Melanoma	RP: To understand the role of V-domain Immunoglobulin Suppressor of T-cell Activation (VISTA) in establishing the immunosuppressive tumor microenvironment. Established that purified VISTA is able to suppress cytokine production by inhibiting toll-like receptor activation, a major pathway in immune cell activation. MR: Melanoma is recognized as one of the rising cancers developed among military personnel, especially field personnel who were exposed to harsh environmental elements such as sun exposure.	*Presentation: 1*
CA130409 $464,034 Open	Abdel-Malek/ University of Cincinnati	Differential Impact of P16 mutations with or without Coexpression of MC1R Mutation on the UV Response of Melanocytes, and Hence on the Risk for Melanoma	RP: To determine the mechanisms by which co-expression of mutations in p16 and loss-of-function allelic variants of MC1R synergistically increase the risk for melanoma. Tested the impact of three mutations in p16 that are present in familial melanoma cases on melanocyte transformation in the absence or presence of non-functional MC1R. Found that heterozygosity for p16 mutations are not enough to affect UV exposure sensitivity within these cells. MR: Understanding the underlying mechanisms that predispose populations to melanoma will be of considerable importance for Service men and women stationed in environments with high UV exposure.	*Funding obtained: 1 grant*

Log Number/ Amount/ Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Melanoma/Skin Cancer				
CA130414 $508,500 Open	Bernstein/ Mount Sinai School of Medicine	Identifying Epigenetic Modulators of Resistance to ERK Signaling Inhibitors	RP: To decipher the epigenetic mechanisms underlying melanoma drug resistance by mapping the epigenomic landscape of melanoma cells that have acquired resistance to ERK signaling inhibitors. Research has revealed novel and critical epigenetic regulators of resistance to RAF inhibitors and RAF inhibitors in combination with MEK inhibitors. Validation experiments are underway. MR: Cutaneous malignant melanoma, the most lethal form of skin cancer, arises from the pigment-producing cells known as melanocytes and is mainly due to sun exposure, which is a military relevant risk factor.	*None to date*
CA130537 $368,031 Open	Khanna/ University of Connecticut Health Center, Farmington	Development of Cytomegalovirus-Based Vaccines against Melanoma	RP: To develop and test the efficacy of cytomegalovirus-based vaccines (CMV)-based anti-melanoma vaccines expressing multiple tumor antigens and to determine the mechanisms of protective immunity provided by these vaccines. Initial studies showed that CMV expressing tumor antigens can generate potent, long-lasting antitumor immunity due to recruitment of CD8+ and CD4+ T-cell recruitment. MR: Deployment to areas of high UV exposures puts Service members at increased risk for the development of melanoma and other skin cancers. This study may lead to new therapeutics to combat melanoma, which can improve the survival and quality of life of the impacted personnel.	*Publications: 2* *Funding obtained: 3 grants*
CA140020 $489,199 Open	Cui/ Boston University Medical Campus	Dot1L is a Lineage-Specific Tumor Suppressor in Melanocyte	RP: To determine the role of Dot1L in melanoma development as well as understanding its function in UV-induced DNA damage and repair. MR: Individuals that serve in tropical areas that receive heavy sun exposure during their early adulthood may be at higher risk of developing melanoma later in life.	*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				
CA140189 $554,400 Open	Fourcade/ University of Pittsburgh	Role of the Inhibitory Receptor TIGIT in the Regulation of CD4+ Tregs in Patients with Advanced Melanoma	RP: This study will assess the role of the inhibitory receptor TIGIT on suppressing the anti-tumor response of the immune system. Observations will be made regarding the effect that small molecules targeting key players in the TIGIT signaling pathway have on the anti-tumor response. MR: UV radiation has been identified as one of the strongest environmental factors for melanoma development. With a significant number of military personnel serving in regions of intense sun exposure, improved therapies will provide higher quality of life for military members and their families.	*New research – no outcomes reported to date*
CA140203 $552,629 Open	Lund/ Oregon Health & Science University	Melanoma-Associated Lymphangiogenesis, Immune Suppression, and Response to Targeted Therapy	RP: This study aims to better understand the immunosuppressive cross-talk between the local T-cell environment and the lymphatic vessels in patients and mouse models. MR: Melanoma incidence in the Caucasian active duty military population has increased rapidly from 1990-1994 to 2000-2004. This increase may be due to significant UV exposure during deployment.	*New research – no outcomes reported to date*
CA140216 $460,477 Open	Harbour/ University of Miami Coral Gables	Development of Targeted Molecular Therapy for Cancers Harboring BAP1 Mutations	RP: Utilize an in vivo high-throughput screen to identify compounds that rescue a developmental phenotype that results from the loss of tumor suppressor gene, BAP1. Promising compounds will also be validated against a mouse model of BAP1-deficienct 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.	*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				
CA140238 $547,200 Open	Su/ University of North Carolina at Chapel Hill	Central Tolerance Blockade to Augment Checkpoint Immunotherapy in Melanoma	RP: Develop an antibody that would enhance the effect of cell cycle checkpoint inhibitors when used in combination against melanoma growth in mice. MR: UV irradiation and other melanoma-predisposing agents are often unavoidable during military deployment. An improvement in immunotherapy for advanced melanoma would benefit military personnel affected by melanoma and other skin cancers.	*New research – no outcomes reported to date*
CA140389 $391,766 Open	Siegel/ McGill University	Development of Rational Combination Therapy Strategies for the Treatment of Metastatic Melanoma	RP: Determine whether an antibody-drug conjugate can be employed in combination with current kinase inhibitor therapy to overcome therapeutic resistance in animal models of metastatic melanoma. MR: Improved therapeutic strategies would benefit military personnel who may be at high risk for melanoma due to environmental exposures.	*New research – no outcomes reported to date*
CA140415 $283,166 Open	Kimlin/ University of the Sunshine Coast	Is Vitamin D Status at Time of Melanoma Diagnosis Associated with Stage of Tumor?	RP: A correlative study to investigate the association between vitamin D levels and tumor characteristics. MR: Active duty personnel in the military receive high exposure to solar UV radiation due to their training and deployment in sunny environments, increasing their risk of melanoma.	*New research – no outcomes reported to date*
CA140485 $474,000 Open	Andarawewa/ University of Virginia	The Therapeutic Effects of Ultrasound-Mediated Immune Responses in Melanoma	RP: A study to determine the utility of a new targeted therapy, focus ultrasound, in stimulating the immune response to tumors in an animal model of melanoma. MR: The incidence of melanoma is higher in the military population in comparison to the general. Improvement to the current standard of care would therefore benefit military families.	*New research – no outcomes reported to date*

Log Number/ Amount/ Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Melanoma/Skin Cancer				
CA140666 $447,000 Open	Xie/ University of Georgia	Treating Melanoma Metastases with a Novel Photodynamic Approach	RP: Evaluate the efficacy of X-ray-inducible photodynamic therapy for metastatic melanoma. This new treatment method will be characterized in vitro as well as within a mouse model of lung metastasis. MR: Melanoma incidence rate is roughly 62% greater in active duty military as compared to the general population. A new treatment for this disease would greatly benefit military personnel and their families.	*New research – no outcomes reported to date*
CA140728 $442,152 Open	Krishna/ Cleveland Clinic Foundation	Polyhydroxy Fullerene Sunscreen for Preventing UV-Induced Skin Cancer	RP: The aim of this study is to engineer a new sustained-release sunscreen formulation using polyhydroxy fullerene, a promising new compound for UV-induced cancer prevention. MR: The most aggressive form of UV-induced skin cancer incidence is increasing at a higher rate among young military personnel (40%) versus the general public (7%). A new topical sunscreen product to prevent sun exposure would benefit those individuals for whom sun exposure is unavoidable.	*New research – no outcomes reported to date*
CA140744 $489,165 Open	Shah/ Massachusetts General Hospital	Stem Cell-Loaded Oncolytic Viruses for Metastatic Melanomas	RP: Evaluate the therapeutic potential of a virus-mediated tumor-selective therapy in vitro and in a mouse model of melanoma brain metastasis. 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 locations. Based on this, military men and women face the potential for long-term risk of melanoma.	*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				
CA150055 $631,899 Under Neg	Kadekaro/ University of Cincinnati	Exploring a New Paradigm in Melanoma Prevention	RP: Determine if there is a correlation between reactive oxygen species and the induction of mutagenic DNA lesions within sun-exposed skin. Investigate whether antioxidants can prevent this damage. MR: Service members are at a higher risk of developing melanoma due to their occupational exposure to sunlight and other sources of UV radiation. 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.	*Research not yet initiated*
CA150068 $558,000 Under Neg	Moon/ University of Michigan	A New Vaccination Strategy for Treatment of Melanoma	RP: A study to develop new technology that will induce potent immune responses against primary and metastatic melanoma using melanoma cell lysate loaded nanoparticles. MR: Military personnel may be at high risk for melanoma due to deployment-related exposures to hazardous physical, chemical, and/or biological factors for extended periods, including documented chronic exposure UV radiation, electromagnetic fields, jet fuel, and volatile organic materials.	*Research not yet initiated*
CA150197 $674,932 Under Neg	Zheng/ Massachusetts General Hospital	Role of the Lipid Phosphatase INPP48 in the Development of Resistance to BRAF Pathway Inhibition	RP: Characterize the signaling mechanism underlying the tumor suppressor effects of INPP4B, a lipid modifying protein, in melanoma and elucidate its contribution to the development of resistance to BRAF pathway inhibition. MR: Military Service men and women who work in sun-intense areas may be at an increased risk for developing melanoma. The incidence of melanoma is higher in the military population than the general population.	*Research not yet initiated*

Log Number/ Amount/ Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Melanoma/Skin Cancer				
CA150256 $620,000 Under Neg	White/ Cornell University Ithaca	Defining the Role of Stem Cell Activation in Initiating Melanoma and Melanocytic Tumor Recurrence	RP: Determine if melanocyte stem cell activation by UV light exposure can act as a primary initiator of tumor growth in melanoma prone-skin. Identify cancer propagating cells within melanoma tumors that resist drug treatment and map the molecular events that occur during cellular transformation. MR: Military members recently deployed to Iraq and Afghanistan report excessive levels of sunlight exposure, causing concern for their heightened risk for melanoma.	*Research not yet initiated*
CA150340 $665,999 Under Neg	Yan/ Yale University	Dissecting the Roles of ARID2 Tumor Suppressor in Metastatic Melanoma	RP: Study to determine how putative tumor suppressor ARID2, an epigenetic regulator, controls melanocyte reprogramming and investigate whether targeting another epigenetic regulator RBP2 can be used to treat patients with ARID2 loss. MR: As the risk of melanoma is highly elevated by heavy sunlight exposure for Service members dispatched to areas like Iraq and Afghanistan, results may significantly benefit these Service members and their families.	*Research not yet initiated*
CA150356 $611,214 Under Neg	Gilmour/ Lankenau Institute for Medical Research (LIMR)	Targeting Increased Polyamine Transport of Resistant Melanomas	RP: Investigate the utility of the polyamine transport system as a therapeutic target for drug-resistant melanoma tumor cells. MR: Military personnel, who have a higher melanoma risk than the general population, will benefit from new medical interventions for melanoma.	*Research not yet initiated*

Log Number/ Amount/ Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Melanoma/Skin Cancer				
CA150391 $606,236 Under Neg	Wang/ University of North Carolina at Chapel Hill	Tissue-Engineered Cancer Metastasis to Improve the Abscopal Effect and Cancer Immunotherapy in Melanoma	RP: Use patient-derived cancer cells to induce immunological clearance of tumors. Will engineer 3D melanoma lung metastases from animals and humans and evaluate their utility as immunizing agents. 3D cultures will be lethally irradiated and injected back into cancer-containing host to determine if these cells can stimulate an anti-cancer immune response. MR: Improvements in management of metastatic melanoma may be particularly beneficial to military populations, who are at a higher risk for melanoma than the general population. Melanoma is more common in 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 active duty members of the Armed Services.	*Research not yet initiated*
CA150437 $610,200 Under Neg	Moubarak/ New York University School of Medicine	Functional Role of Epigenetic Regulation in Melanoma Brain Metastasis	RP: Characterize the proteins involved in PHF8 and CHD7-mediated melanoma brain metastasis and determine the utility of these proteins as clinical biomarkers of melanoma. MR: Gaining understanding of mechanisms of metastasis and conception of novel therapies is crucial for advances in patient care for Service members, their families, and other military beneficiaries.	*Research not yet initiated*

Log Number/ Amount/ Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Melanoma/Skin Cancer				
CA150492 $632,000 Open	Zaidi/ Temple University	UV-Induced Epigenetic Field Effect as a Target for Melanoma Therapy and Prevention	RP: Investigate the role of UV irradiation-induced epigenetic changes in melanoma initiation and determine the utility of these changes as biomarkers. MR: UV radiation from the sun is the most ubiquitous environmental carcinogen, and military personnel are especially prone to high level exposure to UV radiation during deployments to areas with high intensities of UV radiation. Understanding the mechanisms and identifying the biomarkers of melanoma susceptibility, initiation, and progression is vital to devising preventive and therapeutic strategies for military personnel as well as the general public.	*Research not yet initiated*
CA150523 $528,815 Under Neg	Thomas/ Georgia Tech Research Corporation	Targeted Immunotherapy for Melanoma	RP: Evaluate whether lymph node drug targeting leveraging a nanoparticle technology can improve melanoma immunotherapy and significantly improve lymph node delivery of currently approved immunotherapy drugs. MR: Melanoma disproportionately affects military personnel.	*Research not yet initiated*

Log Number/ Amount/ Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Melanoma/Skin Cancer				
CA150619/P1/P2 $2,132,675 Under Neg	Herlyn/ Wistar Institute Cooper; Wargo/ University of Texas MD Anderson Cancer Center	Understanding the Immune Biology of Checkpoint Inhibitors to Develop New Strategies for Therapy	RP: Evaluate the efficacy of the combination of two recently approved immune checkpoint inhibitors, Nivolumab and Ipilimumab, in patients with advanced melanoma. Work is accompanying an ongoing clinical trial at the University of Texas MD Anderson Cancer Center. MR: The incidence of melanoma is higher in the military population than the general population, and is expected to increase in active duty populations.	*Research not yet initiated*
CA150630/P1/P2 $2,197,999 Under Neg	Weber/ New York University School of Medicine Gabrilovich; Hu/ Wistar Institute	Myeloid-Derived Suppressor Cells in Checkpoint Protein Inhibition for Melanoma	RP: Evaluate the immunoregulatory activity of DS-8273a, an antibody therapeutic that activates TRAIL-DR5, when administered in combination with nivolumab in subjects with unrespectable Stage III or Stage IV melanoma, and explore the mechanisms by which the TRAIL-DR5 agonistic antibody depletes myeloid derived suppressor cells. MR: Active duty military are at an increased risk of melanoma due to high levels of sunlight exposure during deployment.	*Research not yet initiated*
CA150776 $131,250 Under Neg	Badrinath/ Dana-Farber Cancer Institute	Development of Epitope-Focused Tumor Vaccine to Prevent Escape from Immune Surveillance by the NKG2D Pathway	RP: Optimize a bacteria-based vaccine and evaluate whether it provides protection against subcutaneous melanomas and metastasis in mice. MR: Active duty Service members are often exposed for prolonged periods to UV radiation, which is the major risk factor for the development of malignant melanoma.	*Research not yet initiated*

Log Number/ Amount/ Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Melanoma/Skin Cancer				
CA150796 $124,874 Under Neg	Zhang/ Yale University	Epigenetic Regulation of Histone Demethylase JARID1B in Melanoma	RP: Investigate the mechanism by which JARID1B regulates melanoma stem cells, and provide evidence for whether JARID1B targeting should be based on its demethylase activity or on its interactions with key transcription factors or co-activators such as PGC-1α. MR: Military Service members and Veterans face higher risk for melanoma and other skin cancers.	*Research not yet initiated*
CA150804 $127,125 Under Neg	Ribeiro Muniz/ Icahn School of Medicine at Mount Sinai	Endogenous Alarmins in the Progression of Melanoma	RP: To identify the receptors involved in metalloproteinase 2 (MMP-2) signaling and investigate the mechanisms by which MMP-2 promotes melanoma progression. Inhibitors of MMP-2 will also be developed. MR: Melanoma rates are higher in active duty military personnel when compared to the general population that may be attributed to exposure to sunlight and UV rays.	*Research not yet initiated*
CA150818 $115,500 Under Neg	Hong/ University of California Los Angeles	Melanoma Drug Addiction and Its Therapeutic Implications	RP: A study to characterize a newly described phenomenon in cancer treatment, termed “drug addiction” where melanoma tumor cells become dependent on BRAF and MEK inhibitors after chronic treatment with these common chemotherapeutics. MR: Studies have shown melanoma to be the second most common cancer in the military, with incidents rapidly rising with constant exposure to sunlight and inadequate protection.	*Research not yet initiated*

Log Number/ Amount/ Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Melanoma/Skin Cancer				
CA150852 $80,934 Under Neg	Barkauskas/ Queensland Institute of Medical Research	The Role of Adenosine A2BR in Metastatic Melanoma	RP: Determine the role of adenosine 2B receptor (A2BR) in melanoma metastasis by studying A2BR expression on the tumor cell surface and/or endothelium. Assess the use of tumor-infiltrating immune cell activators in combination with A2BR inhibitors as metastasis preventative therapy. MR: Studies have found that 77% of military personnel report being exposed to bright sunlight for more than 4 hours a day while working, potentially exposing them to high doses of intermittent UV light, which has been shown in preclinical models to drive melanoma metastasis.	*Research not yet initiated*
CA150863 $101,290 Under Neg	Chang/ Memorial Sloan Kettering Cancer Center	A Therapeutic TCR Mimic Monoclonal Antibody for Intracellular PRAME Protein in Melanomas	RP: Investigate the mechanism by which immunological presentation of a peptide specific to melanoma cells (PRAME(300-309)) is initiated. Determine if this peptide may be utilized to develop new immunotherapies. MR: Melanoma incidences are higher in active duty Service members. The knowledge gained from these studies will help design future immunotherapies for the benefit of military personnel.	*Research not yet initiated*
CA150887 $112,125 Under Neg	Daenthanasanmak/ Medical University of South Carolina	Tumor-Specific Th1/Th17 Hybrid Immunotherapy against Established Melanoma	RP: Characterize a novel cell type, hybrid Th1+/Th17+ T-cells, regarding the molecular mechanisms of cell survival in vivo, immunological memory phenotype, stem cell-like phenotype, and cytotoxic function in tumor eradication. MR: Melanoma is one of the deadliest forms of skin cancer, and affects the general population and military personnel alike.	*Research not yet initiated*

Log Number/ Amount/ Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Melanoma/Skin Cancer				
CA150892 $146,250 Under Neg	Li/ Sanford-Burnham Medical Research Institute, La Jolla	Control of Immune Checkpoints by the Ubiquitin Ligase RNF5: Implications for Melanoma	RP: To test whether ubiquitin ligase RNF5 regulates the fidelity of a signaling pathway that regulates immune cell checkpoints. This work will identify novel targets for future melanoma treatment based on controlling RNF5 activity. MR: Melanoma often develops following prolonged sun exposure. Accordingly, exposure of our Service members to sun during deployment puts young men and women at risk for developing melanoma.	*Research not yet initiated*
CA150903 $118,500 Under Neg	Wilson/ University of Virginia	Ligand Expression on Tumor-Associated Vasculature Orchestrates CD8+ T-Cell Infiltration into Tumors	RP: A study to define the association between homing receptor (HR) ligand expression within the tumor vasculature and the presence of tumor-infiltrating lymphocytes (TIL) using human melanoma samples. Methods to modify HR expression will also be investigated. MR: Melanoma commonly occurs in young adults, including active duty Service members frequently overexposed to harmful UV radiation from sunlight. This puts them at a high risk for getting melanoma and other skin cancers.	*Research not yet initiated*

Log Number/ Amount/ Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Mesothelioma				
CA110751 $308,000 POP Exp	Sharma/ University of California, Los Angeles, David Geffen School of Medicine	Mesothelioma Snail-Mediated Modulation of Inflammatory Responses	RP: To determine if Snail knockdown will have an impact on mesothelioma tumor growth, invasion, and migration by modulating the activities of immune effectors and suppressors. Generated three different mesothelioma knockdown cell lines and studied the growth and invasion characteristics of these cells in vitro. Observed reduced tumor growth rate and increased immune cell recruitment with Snail knockdown lines as compared to controls, suggesting that Snail is a critical component in the immune modulation of these malignancies. MR: Asbestos exposure was widespread among Naval personnel even after the 1980s. Malignant mesothelioma has a long lag time of 20-40 years from the initial exposure to the diagnosis of the disease.	*None to date*
CA120102 $256,613 Open	Klein/ VA Medical Center, Minneapolis, MN	Development of Novel p16INK4a Mimetics as Anticancer Therapy	RP: Determination of the structure-function relationships of overlapping peptides derived from p16INK4a that inhibit the activity of CDK4/6. Identified that cell-penetrating p16-derived peptides have good potency against CDK4 and act synergistically with palbociclib. MR: Mesothelioma often arises in military personnel and Veterans who were exposed to asbestos or asbestos-like materials during routine duties or deployment. Mesothelioma is a highly fatal disease that can affect those exposed to asbestos.	*Publication: 1* *Presentations: 5*

Log Number/ Amount/ Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Mesothelioma				
CA120355 $360,000 POP Exp	Yang/ University of Hawaii	Mesothelioma: Identification of the Key Molecular Events Triggered by BAP1	RP: Study of the impact of BAP1 on the release of HMGB1 and other downstream factors and the effect of BAP1 status on the development of mesothelioma. Results suggest that BAP1 appears to limit Ca2+ release from the endoplasmic reticulum, thus inhibiting apoptosis and that this novel and extranuclear function of BAP1 may cooperate with its known nuclear functions to play a role in carcinogenesis. MR: Veterans from all branches of the Armed Forces may be at high risk for mesothelioma due to the widespread use of asbestos in the construction of military vehicles, air craft, ships, and buildings.	*Publications: 9* *Presentations: 10* *Patents: 3*
CA130197 $391,875 Open	Shukla/ University of Vermont	Exosomes in Development and Therapy of Malignant Mesothelioma	RP: To study the role of exosomes, small lipid bound signaling packages, in the development and therapy of malignant mesothelioma to determine whether exosomes secreted from asbestos-exposed human lung macrophages and epithelial cells can transform human mesothelial cells. Initial research indicates that exosomes generated from epithelial cells exposed to asbestos contain a unique proteomic signature that may be responsible for their uptake by mesothelial cells. MR: Military and Veteran populations are at a higher risk of developing mesothelioma due to Service-related exposures to asbestos. Because of the long latency period of development of this cancer, cases will continue to appear in the Veteran and military populations for decades to come.	*None to date*

Log Number/ Amount/ Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Mesothelioma				
CA130248 $508,593 Open	Poznansky/ Massachusetts General Hospital	Development of a Novel Immunotherapy for Malignant Mesothelioma that Combines CXCL12/CXCR4 Blockade with a Mesothelin-Targeted Fusion Protein	RP: To develop a novel immunotherapy approach for malignant mesothelioma that combines a CXCL12/CXCR4 blockade with a mesothelin-targeted fusion protein. Developed two new mouse models of malignant mesothelioma that allow non-invasive monitoring of tumor growth and progression. Further work will utilize these mice in drug treatment studies. MR: Mesothelioma, a cancer induced by respiratory exposure to asbestos, disproportionately affects military personnel. While Veterans represent 8% of the nation's population, they comprise an astonishing 30% of all known mesothelioma deaths that have occurred in the United States.	*None to date*
CA140269 $400,613 Open	Najmunnisa/ University of Florida	Epha2 -/- NK Cell Therapy Against Malignant Pleural Mesothelioma	RP: This study aims to characterize the mechanism of tumor growth inhibition by natural killer (NK) cells lacking the EphA2 gene using a model of malignant pleural mesothelioma. MR: Thirty percent of new cases of malignant pleural mesothelioma are reported in Veterans each year. Due to environment exposures including asbestos, Veterans are at a high risk of developing this fatal disease.	*New research – no outcomes reported to date*
CA140385 $633,056 Open	Zauderer/ Memorial Sloan Kettering Cancer Center	BAP1 Mutations in Malignant Pleural Mesothelioma: Biology, Clinical Phenotypes, Radiotherapy Response, and Target Discovery for Somatic and Germline Mutations	RP: A study to understand the prevalence and association between mutations in the tumor suppressor gene BAP1 and clinical outcomes of mesothelioma. MR: Malignant mesothelioma disproportionately affects active duty Service members and Veterans due to their exposure to asbestos in 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
Mesothelioma				
CA150220 $616,000 Under Neg	Yang/ University of Hawaii	Identification and Validation of Novel Germline DNA Variants Associated to Increased Risk of Malignant Mesothelioma	RP: To identify novel genes whose mutations predispose individuals to malignant mesothelioma. Whole exome sequencing of malignant mesothelioma patients with a genetic history of cancer will be used to identify susceptibility variants and the functional effect of identified mutations will be assessed in asbestos exposed cell lines and mice. MR: The majority of Veterans were exposed to asbestos at some point during their military service in shipyards, aircrafts, etc. Veterans account for nearly one-third of all malignant mesothelioma diagnoses.	*Research not yet initiated*
CA150300 $553,945 Under Neg	Bertino/ University of Hawaii	Preclinical Development of TVAX: An Advanced Multiantigen Vaccine for Therapy and Prevention of Malignant Mesothelioma	RP: To determine the therapeutic efficacy of a multi-epitope immunization platform termed mTvax. Using a mouse model of malignant mesothelioma, T-cell activation, tumor burden, and survival will be assessed in vaccinated mice. Development and evaluation of a human specific mTvax is also proposed. MR: Over 300 products such as valves, brakes, gaskets, cements, adhesives, and pipe coverings containing asbestos were used by the military, primarily by the Navy, making Navy Veterans one of the highest risk groups for developing asbestos-related malignant mesothelioma. It is estimated that one malignant mesothelioma patient out of every four is a former Navy man or shipyard worker.	*Research not yet initiated*

Log Number/ Amount/ Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Mesothelioma				
CA150671/P1/ P2/P3/P4 $1,902,900 Under Neg	Yang; Carbone/ University of Hawaii Pass/ New York University School of Medicine Kanodia/ Cedars-Sinai Medical Center Mak/ University Health Network, Toronto	HMGB1 and Its Isoforms as Biomarkers for Mineral Fiber Exposure and MM Detection	RP: To define the role of HMGB1, a regulator of inflammatory response, within malignant mesothelioma development and progression. Aims to develop new animal models of malignant mesothelioma to assess whether HMGB1 expression is critical for malignant mesothelioma following asbestos exposure and whether disruption of HMGB1 signaling is a viable intervention target. The project will also assess the utility of HMGB1 isoforms as biomarkers of mineral fiber exposure. MR: Over 300 products such as valves, brakes, gaskets, cements, adhesives, and pipe coverings containing asbestos were used by the military, primarily by the Navy, making Navy Veterans one of the most at-risk groups for developing asbestos related malignant mesothelioma. In fact, it is estimated that one malignant mesothelioma patient out of every four is a former Navy man or shipyard worker. Naval Veterans who served from the World War II era 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.	*Research not yet initiated*
CA150787 $74,980 Under Neg	Chee/ University of Western Australia	Characterizing Neo-Antigen T Cell Responses in Mesothelioma Immunity	RP: A study to determine the utility of antigenic markers of malignant mesothelioma as targets for cancer immunotherapies. The work aims to examine the immunomodulatory effect that mesothelioma-specific antigens have after cancer treatment and to assess whether vaccination against these antigens can sensitize malignant mesothelioma to treatment in a mouse model. MR: Active duty Service members have increased risk over the general population of being exposed to asbestos in shipyards, aircrafts, and other military occupations. In the United States, Veterans of the military account for nearly a third of all malignant mesothelioma diagnoses.	*Research not yet initiated*

Log Number/ Amount/ Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Myeloproliferative Disorders				
CA140408 $462,000 Open	Wilson/ University of New Mexico Health Sciences Center	Calreticulin and Jak2 as Chaperones for MPL: Insights Into MPN Pathogenesis	RP: Test the hypothesis of JAK2, MPL, or CALR mutation leads to abnormal signaling and eventually leads to essential thrombocythemia or primary myelofibrosis. MR: Military members are at higher risk for myeloproliferative neoplasms (MPN). The understanding of pathogenesis, diagnosis, and treatment of MPNs will benefit military populations.	*New research – no outcomes reported to date*
CA150085 $565,162 Under Neg	Felices/ University of Minnesota Twin Cities	Enhancing Natural Killer Cell Mediated Targeting and Responses to Myeloid Leukemias	RP: The study aims to enhance the immunotherapeutic value of NK cells against myeloid leukemia. The approach is to create TriKEs that target NK cells to myeloid tumor cells. MR: Exposure to ionizing radiation, chemicals, and other agents during deployment increases the incidence of myeloid malignancies. Novel therapeutic agents that target myeloid malignancies are needed to help the Warfighters combat these diseases.	*Research not yet initiated*
CA150493 $556,200 Under Neg	Fleischman/ University of California Irvine	Inflammation as a Driver of Clonal Evolution in Myeloproliferative Neoplasm	RP: To understand the mechanism that causes excessive tumor necrosis factor alpha (TNFα) production in MPN, and to identify agents to reduce TNFα production. MR: Many Veterans with MPN had radiation or chemical exposures during their military service.	*Research not yet initiated*
CA150529 $696,000 Under Neg	Fraenkel/ Beth Israel Deaconess Medical Center, Boston	Discovering New Drug Targets in Radiation-Induced Myeloproliferative Neoplasms	RP: To perform the first systematic evaluation of genetic alterations in patients with MPN who have previously been exposed to ionizing radiation. MR: Service members have increased exposure to ionizing radiation, which causes damage to the bone marrow. This study will lead to new drug targets to ionizing radiation-induced MPN.	*Research not yet initiated*

Log Number/ Amount/ Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Myeloproliferative Disorders				
CA150767 $125,909 Under Neg	Ghaffari/ Icahn School of Medicine at Mount Sinai	Dual Inhibition of FLT3 and RET Pathways by ON150030 as Novel Strategy for AML Therapy	RP: To test the therapeutic value of a new therapeutic agent, ON150030 for acute myeloid leukemia (AML). MR: This novel agent could be used as an alternative therapy to Service members with AML who do not respond to the current treatment regimen.	*Research not yet initiated*
Neuroblastoma				
CA130153 $630,000 Open	Freeman/ St. Jude Children's Research Hospital	The Development of a Primary Neural Crest Assay for Neuroblastoma Oncogenesis	RP: To rapidly screen for neuroblastoma-causing genes to identify potential therapeutic targets and to further study the role of the gene ARID1A in neuroblastoma tumorigenesis. During the first year of research, the PI optimized neural crest cell culture conditions to vastly improve screening conditions and made gains in understanding the regulatory feedback loop involving N-Myc and ARID1A. MR: The health and welfare of the Force is influenced by the health and welfare of their families. Military missions benefit when the Warfighters' families are healthy and well.	*Presentations: 2*
CA130396 $521,460 Open	Stewart/ St. Jude Children's Research Hospital	Tumor Growth Model with PK Input for Neuroblastoma Drug Development	RP: To develop a comprehensive computational model using pharmacokinetic and pharmacodynamic measurements to predict drug response patterns in neuroblastoma tumors. The PI successfully collected the majority of the requisite data for one therapeutic and has begun constructing the proposed PBPK model. MR: The health and welfare of the Force is influenced by the health and welfare of their families. Military missions benefit when the Warfighters' families are healthy and well.	*Presentations: 2*

Log Number/ Amount/ Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Neuroblastoma				
CA140035 $570,600 Open	Gustafson/ University of California San Francisco	Drugging the AXIN/GSK/MYCN Complex through an Allosteric Transition in Aurora Kinase A in Neuroblastoma and Medulloblastoma	RP: To test the hypothesis that the scaffold protein AXIN is a member of AURKA/MYC complex observed in MYC/MYCN tumors. Additionally, will test the cytotoxic efficacy, and other cellular effects, of an AURKA conformation disruptor. MR: MYC, MYCN, AURKA, and AXIN are prominent drivers of oncogenesis in a wide array of adult and pediatric tumors, including medulloblastoma and neuroblastoma. Novel therapeutics targeting these molecules will provide benefit to military families and beneficiaries affected by pediatric tumors.	*New research – no outcomes reported to date*
CA140114 $402,430 Open	Bollard/ Children's Research Institute at CNMC	Utilizing TGF-beta Resistant Natural Killer Cells for Adoptive Transfer to Overcome Tumor Immune Evasion	RP: Engineer NK cells that cannot be inhibited by TGF-β, then test the efficacy of these cells to expand and persist in vivo and specifically target tumor cells. MR: Several studies have concluded that the incidence of solid tumors is higher among children of Vietnam War Veterans than in the general population. If this project is successful, it could make cord blood-derived TGF-β-resistant NK cells available as an "off-the-shelf" product to high-risk patients with neuroblastoma.	*New research – no outcomes reported to date*
CA140291 $495,000 Open	Takahashi/ University of Southern California	Peptidic Inhibitors of N-myc for Treatment of Neuroblastoma	RP: Design drug-like peptides that bind to N-Myc and test their efficacy in treating neuroblastoma. MR: Service members who have children affected by neuroblastoma would undoubtedly benefit the most from the potential treatment options that arise from this research.	*New research – no outcomes reported to date*

Log Number/ Amount/ Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Neuroblastoma				
CA150634/P1/P2 $1,733,196 Under Neg	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 research is to develop novel therapeutic options for patients with high-risk neuroblastoma based on disrupting the oncogenic functions of deregulated MYCN, either at the mRNA and/or the protein level. The PIs will develop and test the clinical applicability of these first-in-class tool compounds to inhibit MYCN transcription and hasten degradation of the MYCN protein respectively both singly and in combination with currently utilized agents. The long-term goal of this project is to produce durable responses in patients with MYCN-amplified neuroblastoma, both at initial diagnosis and at relapse. MR: Neuroblastoma accounts for nearly 15% of all childhood cancer deaths. The diagnosis and treatment of neuroblastoma exact a heavy emotional and financial toll on military families. 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.	*Research not yet initiated*

Log Number/ Amount/ Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Neuroblastoma				
CA150773 $123,824 Under Neg	Qadeer/ Icahn School of Medicine at Mount Sinai	Investigating the Mechanisms Underlying ATRX Mutant Neuroblastoma	RP: To test the hypothesis that ATRX mutations culminate in epigenetic and transcriptional alterations in neuroblastoma by (1) mapping ATRX-binding sites in wild-type neuroblastoma and compare them to ATRX-mutant protein localization; and (2) investigating genes that are deregulated in ATRX-mutant neuroblastoma that may be contributing to increased migration and invasion. MR: As military families are strongly affected when their children are diagnosed with neuroblastoma, it is imperative to identify novel therapeutic targets to improve clinical outcomes and alleviate the emotional and physical stresses. By interrogating the unexplored epigenetic mechanisms that contribute to aggressive neuroblastoma, anticipated results may lead to rational therapies to better manage the burden of disease.	*Research not yet initiated*
CA150807 $114,000 Under Neg	Xu/ University of North Carolina at Chapel Hill	Exploiting Hypoxia for T-Cell Immunotherapy in Neuroblastoma	RP: Hypoxia is commonly associated with neuroblastoma, and inhibits the function of naïve and central-memory T-cells. However, effector memory T-cells, commonly utilized in immunotherapies, show enhanced proliferation in hypoxic environments. The PI hypothesizes that the proliferation differences are attributed to differential expression of hypoxia inducible factor 1-α (HIF1-α), and proposes to define the mechanisms of this differential expression. He will also explore how this mechanism might be exploited to improve immunotherapy activity. MR: Results could lead to better and safer treatment options for neuroblastoma, and ultimately alleviate the physical and mental burden for active duty Service members and their children who suffer from neuroblastoma.	*Research not yet initiated*

Log Number/ Amount/ Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Pancreatic Cancer				
CA120028 $405,600 Open	Du/ Cornell University, Weill Medical College	RHAMMB Promotes Liver-Specific Metastasis of Pancreatic Neuroendocrine Tumors	RP: To determine the role of EGFR in RHAMMB (receptor for hyaluronan-mediated motility isoform B)-induced liver metastasis and the clinical relevance of RHAMMB in human pancreatic neuroendocrine tumors. Results suggest that RHAMMB induces the liver metastasis of panNETs through EGFR signaling and that RHAMMB is associated with panNET disease progression. MR: Military missions benefit when the military families are healthy and well.	*None to date*
CA130229 $333,878 Open	Brooks/ University of Mississippi	Novel Molecular Targets for KRAS Downregulation: Promoter G-Quadruplexes	RP: To define the formation, regulation, and therapeutic potential of identified G-quadruplexes (G4s) within the KRAS core promoter. During the first year of the award, the PI characterized the biophysical properties of the G4 complexes within the KRAS promoter and began functional studies into how the G4 formations influence promoter activity. MR: Pancreatic cancer is one of the most lethal forms of cancer that affects Service members, Veterans, military beneficiaries, and their families.	*Publication: 1* *Presentations: 5*
CA130288 $415,200 Open	Wolpin/ Dana-Farber Cancer Institute	Comprehensive Evaluation of Altered Systemic Metabolism and Pancreatic Cancer Risk	RP: To identify and understand, via a prospective plasma metabolite profiling study, the metabolic changes that signal the presence of early pancreatic tumors and promote their growth. Thus far, the PI has identified over 4,000 plasma metabolites from 1,500 pancreatic cancer patient and control samples. This dataset will be analyzed to identify metabolites important in pancreatic cancer. MR: Pancreatic cancer is one of the most lethal forms of cancer that affects Service members, Veterans, military beneficiaries, and their families.	*Publication: 1* *Presentations: 17*

Log Number/ Amount/ Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Pancreatic Cancer				
CA130578 $567,000 Open	Tuveson/ Cold Spring Harbor Laboratory	The Early Detection of Pancreatic Cancer in the U.S. Military	RP: To identify serological biomarkers during carcinogen-mediated pancreatic cancer initiation and progression upon exposure to military-relevant environmental carcinogens. After establishing the model systems, preliminary results have identified several biomarker candidates that will be validated in the upcoming year. MR: Pancreatic cancer is one of the most lethal forms of cancer that affects Service members, Veterans, military beneficiaries, and their families.	*Publication: 1*
CA140228 $531,685 Open	Cukierman/ Institute for Cancer Research	Pancreatic Cancers Desmoplasia: The Possible Bridge Impending Nerve Infiltration and Neoplastic Escape	RP: Determine if the neural synapse maintenance protein, G1, promotes and stabilizes neuronal recruitment to pancreatic tumors and promotes metastasis. MR: Risk factors for pancreatic cancer, such as diabetes, poor diet, smoking, etc., are over-represented in both active duty military personnel and Veterans. This study may lead to improvements in pancreatic cancer diagnosis and treatment and benefit the military and Veteran populations.	*New research – no outcomes reported to date*
CA140634 $479,488 Open	Stanger/ University of Pennsylvania	A Cell-Based Approach to Early Pancreatic Cancer Detection	RP: Determine if pancreatic cells circulating in the blood can be used as biomarkers for detecting pancreatic cancer. MR: There is currently no test to diagnose pancreatic cancer at an early enough stage when effective interventions are most likely to work. The creation of such a detection tool would greatly benefit military personnel at risk for 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				
CA140731 $403,459 Open	Der/ University of North Carolina at Chapel Hill	Targeting KRAS for Pancreatic Cancer Treatment	RP: To fully define KRAS dependency of pancreatic tumors and identify the specific pathways that drive KRAS dependency. MR: Pancreatic cancer is currently the fourth major cause of cancer deaths for active duty Service members and their families, with only a 6% 5-year survival rate.	*New research – no outcomes reported to date*
CA140792 $575,997 Open	Curran/ University of Texas MD Anderson Cancer Center	Immunologic Rejection of Pancreatic Cancer without Autoimmune Side Effects	RP: Test the hypothesis that a combination of three antibodies (αCTLA-4, αPD-1, and α4-1BB) can successfully active an immune response against pancreatic cancer. MR: Pancreatic cancer is one of the most lethal forms of cancer that affects Service members, Veterans, military beneficiaries, and their families.	*New research – no outcomes reported to date*
CA150378 $596,502 Under Neg	Dougan/ Dana-Farber Cancer Institute	Directly Conjugated Single-Domain VHHs Targeting MHC Class II Prime T-Cell Responses against Pancreatic Cancer Neoantigens	RP: To date, immunotherapies have largely failed in treating pancreatic cancer patients. The PI plans to implement a novel mechanism to activate CD4+ T-cells outside of the pancreas, in the lymph nodes and spleen, and then have those T-cells infiltrate the pancreatic tumor and cause tumor rejection. MR: Exposure to pesticides such as DDT that were used in Vietnam has been correlated with increased risk of pancreatic cancer. Ionizing radiation and exposure to chemical carcinogens are direct causes of cancer due to their ability to damage DNA, and the mutational load of these cancers tends to be high. Mutational load, and correspondingly the number of potential neoantigens that can be targeted by the immune system, is correlated with the success rate of immunotherapy.	*Research not yet initiated*

Log Number/ Amount/ Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Pancreatic Cancer				
CA150550 $702,893 Under Neg	Iacobuzio-Donahue/ Memorial Sloan Kettering Cancer Center	Somatic Mosaicism for Cancer Predisposition Genes and Pancreatic Cancer	RP: Determine the prevalence of somatic mosaicism for cancer predisposition genes in normal tissues from patients with pancreatic cancer. MR: Military relevant environmental exposures such as Agent Orange have been linked to an increased incidence of a variety of malignancies. Somatic mosaicism may be associated with cancers associated with military relevant environmental exposures.	*Research not yet initiated*
CA150626/P1/ P2/P3/P4 $1,723,395 Under Neg	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: 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 group will test the influence of the BTKI on immune cell subsets and the efficacy of novel immunotherapy regimens combined with BTKI. MR: Results may enable the development of novel combination therapy regimen for military and Veteran populations with pancreatic ductal adenocarcinoma.	*Research not yet initiated*
Pancreatic Cancer				
CA150842 $130,500 Under Neg	Patra/ Massachusetts General Hospital	Decoding Metabolic Programs Underlying Pancreatic Cancer Progression	RP: To study the metabolic alterations in pancreatic cancer cells with mutant GNAS and compare them to pancreatic cancer cells with other defined genetics. In particular, to study how mutations in the GNAS gene deregulate mitochondrial and lipid metabolism, and then study how GNAS-regulated pathways drive alternative metabolic programs. MR: Pancreatic cancer is one of the most lethal forms of cancer that affects Service members, Veterans, military beneficiaries, and their families. This study could identify new therapeutic targets.	*Research not yet initiated*

Log Number/ Amount/ Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Pediatric Brain Tumor				
CA120318 $400,425 Open	Huang/ Cornell University, Weill Medical College	Characterizing and Targeting Bone Marrow-Derived Inflammatory Cells in Driving the Malignancy and Progression of Childhood Astrocytic Brain Tumors	RP: To study the functions of bone marrow-derived inflammatory cells (BMDCs) in the progression of pediatric glioma and develop therapeutic strategies to target a specific population of BMDCs to suppress the malignant transformation of gliomas. Identified a unique population that could potentially be used for glioma diagnosis and prognosis. Validated changes of myeloid and endothelial lineages during glioma progression and observed the increase of myeloid derived suppressor cells and endothelial progenitor cells in murine glioma models. MR: Military missions benefit when military families are healthy and well.	*Publication: 1* *Presentations: 3*
Pediatric Brain Tumor				
CA130273 $522,410 Open	Yun/ Jackson Laboratory	Cell of Origin and Cancer Stem Cell Phenotype in Medulloblastomas	RP: To determine if the biological differences of cells in the developing brain at different stages of maturation, when cancerous, produce medulloblastomas with distinct biological characteristics. Thus far, the PI has created new mouse models in which to test his hypotheses. MR: The health and welfare of the Force is influenced by the health and welfare of their families. Military missions benefit when the Warfighters' families are healthy and well.	*None to date*

Log Number/ Amount/ Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
CA130319 $331,063 Open	Ying/ Hugo W. Moser Research Institute at Kennedy Krieger, Inc.	Modeling Aggressive Medulloblastoma Using Human-Induced Pluripotent Stem Cells	RP: Determined that neural progenitors can be induced from human-induced pluripotent stems cells and form MYC-driven Group 3 medulloblastomas. These medulloblastoma tumors can be cultured in the laboratory, and are now being used to test both new and existing drugs for patients with Group 3 medulloblastoma and further study the MYC-regulated signaling network to identify new therapeutic targets. MR: The health and welfare of the Force is influenced by the health and welfare of their families. Military missions benefit when the Warfighters' families are healthy and well.	*Presentation: 1*
CA130436 $421,077 Open	Hinchcliffe/ University of Minnesota, Twin Cities	Defects in Histone H3.3 Phosphorylation and ATRX Recruitment to Misaligned Chromosomes during Mitosis Contribute to the Development of Pediatric Glioblastomas	RP: Showed that p53 cell cycle arrest triggered by chromosome mis-segregation is mediated via a novel signaling mechanism dependent upon phosphorylation at a specific histone site, and ATRX recruitment to lagging (mis-segregating) chromosomes. These observations suggest a putative mechanism for the formation of glioblastomas. MR: The health and welfare of the Force is influenced by the health and welfare of their families. Military missions benefit when the Warfighters' families are healthy and well.	*Publication: 1* *Presentations: 9*
Pediatric Brain Tumor				
CA140089 $529,200 Open	Friedman/ University of Alabama at Birmingham	Intraventricular Delivery of Engineered Oncolytic Herpes Simplex Virotherapy to Treat Localized and Metastatic Pediatric Brain Tumors	RP: There is a significant need to develop more effective and less neurotoxic treatments for pediatric brain tumors. This project will use a murine model to determine the underlying mechanisms of treatment-induced toxicity and develop strategies that block toxicity while maintaining therapeutic efficacy. MR: Results may expand treatment options for pediatric brain tumors by developing of novel targeted therapies with reduced toxicities, and benefit Service members and their families affected by pediatric brain tumors.	*New research – no outcomes reported to date*
Stomach Cancer				

Log Number/ Amount/ Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
CA150079 $639,556 Under Neg	Bass/ Dana-Farber Cancer Institute	Developing Mouse Models of Stomach Cancer with CRISPR/Cas9 Technologies and Environmental Exposures	RP: To develop mouse model for stomach cancer using CRISP/Cas9 technology toward improved understanding and development of treatments for stomach cancer. MR: Service members are exposed to infectious and chemical agents that increase the risk for stomach cancer. This study seeks to develop technologies that lead to better understanding and treatment for stomach cancer.	*Research not yet initiated*
CA150132 $576,000 Under Neg	Gough/ Monash University	Defining the Efficacy of Blocking Serine Phosphorylated STAT3 in the Treatment of Gastric Cancer	RP: To test the hypothesis that targeting mitochondrial pS727 STAT3 will suppress inflammation-associated tumorigenesis. MR: Service members have a higher rate of *Helicobacter pylori* (*H. pylori*) infection than civilians. Chronic *H. pylori* infection is a major risk factor for stomach cancer. This study will lead to new therapeutic options for stomach cancer and benefit the military community.	*Research not yet initiated*
Stomach Cancer				
CA150252 $575,954 Under Neg	Akbani/ University of Texas MD Anderson Cancer Center	Analysis of Gastric Adenocarcinoma Data in a Pan-GI Context to Reveal Genes, Pathways, and Interactions that Yield Novel Therapeutic Advantages	RP: This study aims to identify genes, pathways, and interactions for gastric cancer by analyzing Pan-GI data. MR: Service members have increased risk for stomach cancer when deployed to regions with higher rate of *H. pylori* infection. This study will expand our knowledge of gastric cancer and could potentially improve treatment options for the military.	*Research not yet initiated*
CA150334 $640,000 Under Neg	Ajani/ University of Texas MD Anderson Cancer Center	Exploiting RhoA Mutations in Diffuse Gastric Adenocarcinoma and Targeting Intertwined RhoA and Yap1 Pathways for Therapeutic Advantage	RP: To test the hypothesis that RhoA and Yap1 pathways are novel targets for diffuse gastric adenocarcinoma (dGAC) and that the dual inhibition will provide added advantage against dGAC. MR: Service members have increased risk for stomach cancer when deployed to regions with higher rate of *H. pylori* infection. This study could lead to new treatment options for stomach cancer.	*Research not yet initiated*

Log Number/ Amount/ Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
CA150357 $388,380 Under Neg	Bao/ Brigham and Women's Hospital	Plasma Metabolomic Fingerprint of Early Gastric Cancer	RP: A study to describe the metabolomics fingerprint associated with gastric cancer. The researcher will measure the individual metabolite levels from patient plasma samples to determine gastric cancer risk. From these data, a definition of the metabolic pathways important in development and maintenance of gastric cancer will be generated. MR: Gastric cancer is a Service-connected malignancy for Service members who experienced hazardous exposure to ionizing radiation. In addition, research has shown that U.S. Soldiers living under field conditions are at great risk of *H. pylori* infection, which is the main cause of gastric cancer.	*Research not yet initiated*
Stomach Cancer				
CA150375 $607,557 Under Neg	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. Stomach cancer is one of the top cancers treated in the VA system.	*Research not yet initiated*
CA150646/P1/P2 $2,081,946 Under Neg	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 micro RNAs (miRNAs) contribute to drug resistance in HER2-positive EG. MR: EG incidence is rapidly increasing and has high impact on the military and Veteran populations.	*Research not yet initiated*

Log Number/ Amount/ Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
CA150647/P1/ P2/P3/P4 $1,931,391 Under Neg	Korn; Collisson; Fong; Ashworth/ University of California San Francisco Janjigian/ Memorial Sloan Kettering Cancer Center	Targeting BRCAness in Gastric Cancer	RP: To test a combination therapy using immunotherapy and PARP inhibition to treat gastric cancers displaying BRCAness. MR: Service members are exposed to higher risks of *H. pylori* infection and radiation exposure resulting in increased risk of gastric cancer.	*Research not yet initiated*
Stomach Cancer				
CA150742 $89,700 Under Neg	Sung/ National Cancer Institute	Discovery and Validation of Plasma DNA Methylation Biomarker for Detection of Stomach Cancer	RP: To identify and validate plasma DNA methylation as a potential biomarker for the detection of stomach cancer. Will use blood samples from patients and case-control subjects to identify and test biomarker utility. MR: If shown to be valid, these biomarkers, which are based on a simple blood test, have the potential to transform stomach cancer screening and reduce disease-related mortality in the general public as well as in military members, Veterans, and their families.	*Research not yet initiated*
CA150895 $131,250 Under Neg	Zhang/ Dana-Farber Cancer Institute	The Function of RHOA Mutations in the Development of Diffuse Gastric Cancer	RP: To test the hypothesis that genomic perturbation of the RHO pathway complements the effect of CDH1 (cadherin-1) inactivation to promote the formation of diffusive gastric cancer. MR: Service members are exposed to higher risks of *H. pylori* infection and radiation exposure, resulting in increased risk of gastric cancer.	*Research not yet initiated*

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APPENDIX A: FISCAL YEAR 2009 (FY09)-FY14 RESEARCH PROGRESS AND MILITARY RELEVANCE OF CLOSED AWARDS

Log Number/ Amount/ Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Blood Cancer				
CA100164 $545,036 Pending Closeout	Trobridge/ Washington State University, Pullman	Identification of Biomarkers for Myelodysplastic Syndrome (MDS) and Acute Myeloid Leukemia (AML) Using a Novel High-Throughput Forward Mutagenesis Screen	RP: Mutagenesis screen and drug development study for biomarkers of myelodysplastic syndrome (MDS) and acute myelogenous leukemia (AML). Generated MDS and AML transplanted mice for biomarker screening. Identified a candidate gene that is differentially expressed in AML patients. MR: Military personnel are at risk of exposure to alkylating agents, in the form of chemical weapons, and ionizing radiation, from nuclear and/or radioactive sources, that can cause therapy-related AML (t-AML)/therapy-related MDS (t-MDS).	*Publication: 1* *Presentations: 2* *Patent: 1 provisional patent*
CA100254 $440,220 Closed	Sarantopoulos/ University of North Carolina at Chapel Hill	BAFF-Driven Targeted Immunotherapy for Patients with Leukemia	RP: Study on how BAFF (B-cell activating factor) promotes specific anti-leukemia responses to develop novel therapeutic agents for leukemia. Established two murine leukemia models. Identified B-cell subsets related to chronic graft versus host disease and graft versus leukemia. MR: The environmental exposure to cytotoxins and chemicals during deployment is associated with higher incidence of leukemia.	*Presentation: 1* *Funding obtained: 1 grant*

Log Number/ Amount/ Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Blood Cancer				
CA100623 $1,073,580.38 Closed	Lanza; Tomasson/ Washington University	Treatment of Multiple Myeloma with VLA4-Targeted Nanoparticles Delivering Novel c-MYC Inhibitor Prodrug	RP: Develop nanoparticle encapsulated prodrug to inhibit Myc and test its efficacy on multiple myeloma (MM). The Myc prodrug markedly improved bioactivity in several myeloma cell types. The prodrug extended the days of survival of mice with metastatic myeloma by 50%. MR: Male Veterans using VA hospitals are at 51% increased risk of MM compared to the general public.	*Publications: 2* *Presentations: 44*
CA110020 $242,777.96 Pending Closeout	Masamha/ University of Texas Health Science Center at Houston	Deciphering the Mechanism of Alternative Cleavage and Polyadenylation in Mantle Cell Lymphoma (MCL)	RP: Study the mechanism of cyclin D1 mRNA alternative cleavage and polyadenylation in Mantle Cell Lymphoma. Identified CFIm25 as a global regulator of polyadenylation for over 1,400 genes including cyclin D1. CFIm25 depletion corresponds with enhanced tumorigenicity. MR: The environmental exposure to cytotoxins and chemicals during deployment is associated with a higher incidence of blood cancers.	*Publication: 1 (Nature)* *Presentation: 2*
CA110081 $369,468.69 Pending Closeout	Newman/ Stanford University	Genomic Signatures for Integrative Models of Clinical Heterogeneity in Patients with Follicular Lymphoma	RP: Development of a novel method to determine follicular lymphoma patients' responsivity to treatment. Developed a novel computational method to validate therapeutic response. MR: The environmental exposure to cytotoxins and chemicals during deployment is associated with a higher incidence of blood cancers.	*Publication: 1* *Presentations: 2*

Log Number/ Amount/ Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Blood Cancer				
CA110096 $218,526.12 Closed	McClellan/ Stanford University	Reprogramming of Human Acute Lymphoblastic Leukemia Cells by Myeloid Transdifferentiation	RP: Reprogram human B cell acute lymphoblastic leukemia (B-ALL) cells in vitro to characterize the genes to determine if triggers for disease regression. MR: The environmental exposure to cytotoxins and chemicals during deployment is associated with a higher incidence of blood cancers.	*Publication: 1* *Presentation: 1*
CA110584 $262,647.71 Closed	Reuther/ H. Lee Moffitt Cancer Center & Research Institute	Enhancing Targeted Therapy for Myeloproliferative Neoplasms	RP: Focuses on the molecular targeted therapy for myeloproliferative neoplasms and how it can be enhanced by combination therapy with modulators of lipid biosynthesis. MR: The environmental exposure to cytotoxins and chemicals during deployment is associated with a higher incidence of blood cancers.	*None*
CA110791 $310,965.72 Pending Closeout	Wei/ University of Texas MD Anderson Cancer Center	Innate Immunity Dysregulation in Myelodysplastic Syndromes	RP: Demonstrated that TLR2 innate immune signaling is excessively activated in MDS bone marrow stem/progenitor cells. Led to a Phase I/II clinical trial to assess the antibody OPN-35 in MDS patients. MR: Military personnel are at risk of exposure to alkylating agents, in the form of chemical weapons, and ionizing radiation, from nuclear and/or radioactive sources, that can cause t-AML/t-MDS.	*Publications: 3* *Presentations: 6*
CA110834 $200,000 Pending Closeout	FitzGerald/ National Cancer Institute	Anti-CDR3 Therapy for B-Cell Malignancies	RP: Devise a proof-of-concept method for rapidly producing B-cell cancer-specific immunotherapy molecules customizable to individual patients. Cloned, sequenced, and engineered the variable region of two surface immunoglobulin molecules. MR: The environmental exposure to cytotoxins and chemicals during deployment is associated with a higher incidence of blood cancers.	*None*

Log Number/ Amount/ Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Blood Cancer				
CA120025 $415,470 Pending Closeout	Reagan/ Dana-Farber Cancer Institute	Reciprocal Interactions between Multiple Myeloma Cells and Osteoprogenitor Cells Affect Bone Formation and Tumor Growth	RP: Developed a bone cancer model that supports long-term culture and imaging of myeloma cells, high-throughput drug screening, vessel formation, and osteogenesis in the presence of cancer. MR: MM is a disease of particular relevance to our military Veterans. Male Veterans using VA hospitals are at 51% increased risk of MM compared to the general public.	*Publications: 2* *Presentations: 5*
CA120120 $344,007 Pending Closeout	Xie/ Rutgers, State University of New Jersey	Regulation of Mitochondria Function by TRAF3 in B Lymphocytes and B-Cell Malignancies	RP: Study the role of mitochondria in TRAF3, novel tumor suppressor, induced apoptosis in B cells. MR: This study seeks to find new avenues for the prevention and treatment of major blood cancers, which impact many military personnel.	*Publications: 2* *Presentations: 4*
CA120184 $397,693 Pending Closeout	Lin/ Dana-Farber Cancer Institute	Understanding Selective Downregulation of c-Myc Expression through Inhibition of General Transcription Regulators in MM	RP: Demonstrated selective downregulation of c-Myc expression through inhibition of general transcription regulators in MM. MR: MM is a disease of particular relevance to military Veterans. Male Veterans using VA hospitals are at 51% increased risk of MM compared to the general public.	*Publications: 5* *Presentations: 2* *Software: 1 database, 1 software tool* *Employment: The PI obtained a faculty position*
CA120373 $374,400 Pending Closeout	Liu/ Indiana University, Indianapolis	Modulating Leukemia-Initiating Cell Quiescence to Improve Leukemia Treatment	RP: Determined the role of Necdin in the initiation of AML and characterized whether lowered Necdin expression affects the response of leukemia-initiating cells to chemotherapy or radiotherapy. MR: This study seeks to understand how Necdin functions in normal and leukemic stem cells, which may lead to innovative clinical applications and benefit those military personnel impacted by the disease.	*Publications: 10* *Presentations: 19*

Log Number/ Amount/ Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Colorectal Cancer (CRC)				
CA100111 $313,725 Pending Closeout	Jessup/ National Cancer Institute	Inhibition of Embryonic Genes to Control Colorectal Cancer Metastasis	RP: Confirmed that NANOG is a significant prognostic factor as it is expressed in the majority of primary human colon carcinomas. Determined that NANOGP8 inhibition induces apoptosis through inhibition of MCL-1. MCL-1. Also showed that vector-delivered shRNA to NANOGP8 can inhibit BCL-2 and BCL-XL to kill CRC cells. MR: CRC is the second highest cause of cancer-specific mortality in the U.S. population. Approximately 50% of military personnel and dependents who are diagnosed with colon or rectal carcinoma will die of the disease.	*Publications: 2* *Presentations: 7* *Patent application: 1*
CA100512/P1 $1,076,301 Pending Closeout	Eckhardt; Tan/ University of Colorado Denver	Collaborative Model for Acceleration of Individualized Therapy of Colon Cancer	RP: Three novel anti-cancer agents have been identified to develop predictive classifiers using preclinical CRC models. MR: The largest segment of the military, white males, has an incidence rate of 53/100,000, whereas black males have a higher incidence (and mortality) of 63/100,000.	*Publications: 3* *Presentations: 8*
CA100879 $592,307 Pending Closeout	Ellis/ University of Texas MD Anderson Cancer Center	Microenvironmental Influence of Endothelial Cells on Colorectal Cancer Stem Cell Phenotype	RP: Study into the interactions of inflammation, endothelial cells, cancer stem cells (CSCs) and chemoresistance development. Identified and confirmed that soluble JAG1, a paracrine factor of endothelial cells regulates CSC phenotype in CRC cells by secreting soluble Jagged-1, via ADAM17 proteolytic activity, leading to Notch activation in CRC cells. Found that macrophages had a direct CSC-promoting effect that is not mediated by JAG1. MR: The understanding of critical pathways to resistance will support military cancer treatment of Service members and their families.	*Publications: 2 (one in Cancer Cell)*

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

Log Number/ Amount/ Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Colorectal Cancer (CRC)				
CA110495 $341,040 Closed	Kufe/ Dana-Farber Cancer Institute	Targeting of the MUC1-C Oncoprotein in Colitis-Associated Colorectal Cancer	RP: To explore the mechanisms responsible for the progression of inflammatory bowel disease to CRC for new strategies for drug development. Results indicated that MUC1-C is important mechanistically as a link between intestinal inflammation and CRC progression and represents a potential therapeutic target. MR: CRC is the second highest cause of cancer-specific mortality in the general public and military population.	*Publication: 1*
CA120206 $238,515 Pending Closeout	MacNeill/ Wake Forest University Health Sciences	Electrically Conducting Polymer Nanoparticles to Selectively Target and Treat Metastatic Colorectal Cancer	RP: Aims to synthesize a new nanoparticle-drug conjugate for targeted photothermal ablation of CRC and demonstrate its therapeutic potential in mice. Development of near-infrared phototherapy using electrical conducting polymer nanoparticles to treat colorectal cancer. Demonstrated that a low band gap D-A conjugated polymer P3, that absorbs in the NIR (~800 nm), can be fabricated into spherical nanoparticles (nano-P3) using Pluronic F127 as a soft template. MR: Only 58% of military men and women who should be screened for CRC have been screened. This number is low compared to the general population and contributes to the fact that CRC is one of the most common forms of cancer among active military personnel.	*This Visionary Postdoctoral Award ended early as the PI secured a permanent position at L'Oreal USA (New Jersey)*

Log Number/ Amount/ Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Colorectal Cancer (CRC)				
CA120261 $363,411 Pending Closeout	LaBarbera/ University of Colorado Denver, Anschutz Medical Campus	Novel Antimetastatic Agents for the Treatment of Drug-Resistant and Metastatic Colon Cancer	RP: A study to develop analogues to a natural product that inhibits gene expression patterns that promote metastasis. Using rational drug design based on the 3D structure of the target protein, TopoIIa, compounds were synthesized and tested for antitumor activity in vitro and in vivo. From the initial cohort of compounds, one derivative showed inhibition of TopoIIa activity and increased efficacy on in vivo tumor growth as compared to the original lead compound. MR: Active military personnel, Veterans, and family members are at considerable risk for CRC. Novel therapies that target TCF transcription may prevent metastasis and recurrence of CRC.	*Presentations: 18* *Publications: 5* *Patent: 1*
Genetic Cancer				
CA093054 $113,319 Closed	Lantz/ University of Arizona, Tucson	The Carcinogenic Potential of JP-8 and Tungsten in C57BL/6 Mice	RP: The study of environmental exposures (JP-8 and tungsten) known to be a health risk for Service members. The project included interactions with viral infections, which may lead to long-term health consequences such as cancer development. Found that JP-8 alone did not cause reactivation of Epstein-Barr virus (MHV-68), yet the combination of tungsten and other environmental agents with in utero exposure was able to prime the immune system for aberrant response to infectious agents. MR: Military personnel encounter environmental exposures related to their service that risk long-term health care issues, e.g., leukemia clusters.	*Publication: 1* *Presentations: 2* *Employment Opportunities: 3*

Log Number/ Amount/ Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Genetic Cancer				
CA093111 $115,500 Closed	Yennu-Nanda/ University of Texas MD Anderson Cancer Center	Role of Melanin in Oncogenesis	RP: This study tested the hypothesis that melanin itself can cause melanoma. Results showed the induction of excessive melanin production leads to changes in gene expression profiles dependent on skin type and suggest that long-term melanin induction may increase the transformation of melanocytes with low basal melanin levels as compared to those with high basal levels. MR: The prevention and early diagnosis modalities for skin cancers will be of immense benefit to U.S. Soldiers on the frontlines, and in theater where high ultraviolet (UV) exposures increases risks.	*None*
CA093139 $559,548 Closed	Cao/ Clemson University	New Protein Modification under Nitrosative Stress	RP: Reactive nitrogen species leads to unstable DNA and carcinogenesis. Treatment of endonuclease V resulted in decreased DNA repair activity. MR: Explosions and blasts occurring in battlefield intensify the contacts of military personnel with gaseous reactive nitrogen species and may inflict acute and chronic impact on the health of military personnel.	*Publications: 3*

Log Number/ Amount/ Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Genetic Cancer				
CA093155 $109,875 Closed	Wallis-Schultz/ Texas A&M University	Functional Genomics Screen for Radiation Responsive Genes in Mutant Mouse Embryonic Stem Cells	RP: Identification of candidate genes responsible for cellular response to radiation exposure. This project involved the search for genes that affect the cellular response to radiation exposure and led to the identification and validation of seven differentially expressed candidate genes. These genes and their pathways could then be targeted to enhance resistance, treat exposure, improve radiation therapy for those with cancer, or serve as diagnostic or pharmacogenetic biomarkers. MR: Armed forces members are occupationally at higher risk for exposure to carcinogenic radiation sources such as excessive sunlight and depleted uranium. Military exposures and risks include radiation exposures, which have long-term health risk factors and outcomes.	*None*
CA093176 $111,301 Closed	Su/ Drexel University	Development of a Genetic Urine Test Using a Padlock-Mediated Microarray for Colon Cancer Screening	RP: Development of a non-invasive, genetic-based CRC biomarker screen using a padlock-mediated microarray to analyze urine. The screen was able to detect a promising CRC DNA marker, the abberant hypermethylation of the vimentin gene, in the urine of patients with CRC through a blinded study MR: Technological advances supported by the military increase the ability of military medicine to answer the needs of Service members and their families and decrease general health care costs to the military.	*Publication: 1* *Patent: 1* *Presentation: 1*

Log Number/ Amount/ Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Genetic Cancer				
CA093193 $109,125 Closed	Elble/ Southern Illinois University	A Novel Therapy for Metastatic Melanoma	RP: Study of the CLCA2 tumor suppressor as a gene therapy candidate for the prevention and treatment of melanoma. Demonstrated that restoration of CLCA2 expression is lethal to melanoma cells. MR: Deployment to areas of high UV exposures puts Service members at increased risk for the development of melanoma and other skin cancers.	*Presentation: 1*
CA093204 $109,399 Closed	Yusuf/ University of Alabama at Birmingham	Role of p16/INK4a in Ultraviolet Radiation-Induced Inflammation and Photocarcinogenesis	RP: To study the role of p16 in UVB radiation-induced inflammation and skin tumor development. Results indicate that p16/INK4a deficiency does lead to inflammation and associated cutaneous tumor development. MR: Deployment to areas of high UV exposure puts Service members at increased risk for the development of melanoma and other skin cancers.	*Presentation: 1*
CA093257 $96,750 Pending	Chen/ Southern California Institute for Research and Education	Monitor microRNA Expression in Blood and Saliva to Detect Radiation-Induced Cancer Progression	RP: Development of a blood and/or saliva biomarker test for radiation-induced lymphomas. Determined that there is a stable baseline of serum miRNA profiles that can allow for the possible detection of changes associated with radiation-induced lymphoma. MR: Military personnel are at higher risk of radiation exposures related to their service and therefore development of long-term health issues such as lymphomas and leukemias.	*Presentation: 1*

Log Number/ Amount/ Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Genetic Cancer				
CA093269 $115,875 Closed	Ongkeko/ University of California, San Diego	Tobacco and Nicotine Promote Acquisition of Cancer Stem Cell Properties in Head and Neck Cancer	RP: Study of the impact of nicotine and smoking on cancer stem cells. Determined that long-term nicotine exposure generates cells with cancer stem cell-like properties that were demonstrated to have a greater capacity for survival with a higher tendency towards invasion. This suggested that nicotine could play a crucial role in the development of tobacco-induced cancers by regulating stem cell characteristics through epithelial-to-mesenchymal promoting, microRNA-mediated pathways. MR: Military personnel have a higher level of cigarette smoking than the general population. Nicotine and tobacco smoking is a risk factor for head and neck cancer.	*Presentation: 1*
CA093337 $114,500 Pending Closeout	Kitlinska/ Georgetown University	Neuropeptide Y: A New Link between Stress and Cancer	RP: Examination of the role of chronic exposure to psychological and physical stress on cancer progression via release of neuropeptide Y. Potent effects of neuropeptide Y and other stress mediators on tumor development and progression have been demonstrated in mouse models of multiple cancer types. MR: Understanding the role of post-traumatic stress disorder and chronic stress in potential future cancer development of Veterans is an important area of research.	*Publication: 1* *Presentations: 2*
CA093377 $383,315 Closed	Armani/ University of Southern California	Real-Time Detection of DNA Methylation	RP: Development of a new tool to detect epigenetic changes in response to environmental factors that the Service members encounter. The PI demonstrated sensor design, instrument design, surface chemistry of labeling, and detection of methylated DNA. MR: Radiation exposure is of high risk in military populations.	*Publications: 3* *Presentations: 11* *Funding obtained: 2*

Log Number/ Amount/ Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Genetic Cancer				
CA093395 $560,148 Closed	Brooks/ Maine Medical Center	UV-Induced Triggering of a Biomechanical Initiation Switch within Collagen Promotes Development of a Melanoma-Permissive Microenvironment in the Skin	RP: The study showed that UV radiation of extracellular matrix proteins altered the adhesion, migration, and proliferation of fibroblast, melanoma cells, and macrophages in vitro. UV exposure of mouse skin induced inflammation and exposure of the HU177 cryptic collagen epitope. MR: Deployment to areas of high UV exposure puts Service members at increased risk for the development of melanoma and other skin cancers.	*None*
CA093415 $428,999 Closed	Hu/ University of Medicine and Dentistry of New Jersey, Robert Wood Johnson Medical School	Psychological Stress Promotes Irradiation-Induced Tumorigenesis through Attenuation of p53 Function	RP: This study provides a direct link between chronic stress and tumorigenesis in mouse models. Major findings include: chronic stress promotes IR-induced tumorigenesis; and chronic stress elevates glucocorticoids, negatively regulates p53 function, and promotes tumorigenesis. MR: Understanding the role of chronic stress and radiation exposure for potential future cancer development in the Veteran population is of significant military relevance.	*Publications: 7 (including one in Nature Communications)* *Presentations: 2* *Funding obtained: 1*
CA093417 $404,299 Pending Closeout	Yusuf/ University of Alabama at Birmingham	Regulation of Ultraviolet Radiation-Induced Cutaneous Photodamage and Nucleotide Excision Repair by Toll-Like Receptor-4	RP: Found that Toll-like Receptor 4 (TLR4) deficiency enhanced DNA repair in mouse skin after UVB exposure; cytokine IL-2 had a significant effect on repairing cyclobutane pytimidine dimmers in TLR4 knockout mice. MR: Deployment to areas of high UV exposures puts Service members at increased risk for the development of melanoma and other skin cancers.	*Publication: 1*

Log Number/ Amount/ Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Genetic Cancer				
CA093422 $404,849 Closed	Jimeno/ University of Colorado Denver	The XactMice: A Xenochimaeric Mouse with Tumor and Hematopoietic System Obtained from the Same Patient	RP: Development of mouse model to better understand carcinogenesis and its treatment. Demonstrated the feasibility of engrafting human tumors on humanized mice. The humanized and non-humanized tumor expression profiles will be made available to public. MR: Advancing genetic research has a direct application to active, reserve, and retired U.S. Service members and their families, since military lifestyle entails potential exposure to carcinogens known and presumed, chemical and physical/radioactive in nature, both in training and in deployment, and related to equipment utilization and/or combat.	*Publication: 1* *Patent: 1 US patent application*
CA093492 $657,517 Closed	Testa/ Fox Chase Cancer Center	Role of the Inflammasome in Asbestos-Induced Mesothelioma Formation	RP: Study of the role of NALP3 inflammsome and the development of mesothelioma due to asbestos exposure. Demonstrated the genetic link between asbestos-associated inflammation and the development of malignant mesothelioma. Found targeting IL-1β signaling with IL-1R antagonist results in delayed asbestos-induced MM onset and progression. MR: Asbestos exposure was widespread among Naval personnel even after the 1980s. Malignant mesothelioma has a long lag time of 20-40 years from the initial exposure to the diagnosis of the disease. Long-term risk of mesothelioma development following asbestos exposures is critical for U.S. Veterans and active military.	*None*

Log Number/ Amount/ Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Genetic Cancer				
CA093544 $653,132 Closed	Cantor/ Children's Hospital, Boston	Runx-1-Centered Transcriptional Pathways as Tools to Discover Novel Genetic Risk Factors for Radiation-Induced Myelodysplastic Syndrome and Leukemia	RP: Identified 5'UTR mutations in ANKRD26 gene as a novel cause of leukemia predisposition and thrombocytopenia in humans. Identified a role of 5'UTR in DNA repair and chromosome segregation and connected it to two leukemia factors, Menin and MLL. MR: Advancing genetic research has a direct application to active, reserve, and retired U.S. military personnel and their families as a military lifestyle entails potential exposure to carcinogens known or presumed, chemical and physical/radioactive in nature, both in training and in deployment, and related to equipment utilization and/or combat.	*Presentations: 3* *Funding obtained: 1*
CA093566 $423,038 Closed	Dai/ Oregon Health & Science University	Regulation of c-Myc mRNA by L11 in Response to UV and Gamma Irradiation	RP: Demonstrated that ribosomal protein L11 regulates c-Myc, and elucidated the mechanism of ribosomal biogenesis and c-Myc activity under radiation stress conditions. MR: Exposure to environmental hazards in military personnel is associated with increased cancer risks. Studies of hazardous exposures that may cause damage to DNA and long-term health care issues such as cancer are beneficial to military personnel.	*Publications: 4*
CA093573 $449,979 Closed	Majeti/ Stanford University	Genetic Characterization of Leukemia Stem Cells in Chemical- and Radiation-Induced Acute Myelogenous Leukemia	RP: Identification and molecular characterization of leukemia stem cells from mouse models of t-AML/t-MDS (therapy-related acute myelogenous leukemia/therapy-related myelodysplastic syndrome) induced by alkylating agents or ionizing radiation. Established a mouse model of radiation-induced t-AML/t-MDS. MR: Military personnel are at risk of exposure to alkylating agents, in the form of chemical weapons, and ionizing radiation, from nuclear and/or radioactive sources, that can cause t-AML/t-MDS.	*None*

Log Number/ Amount/ Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Genetic Cancer				
CA093588 $631,258 Closed	Tsao/ Massachusetts General Hospital	Governance of Cutaneous Photocarcinogenesis by Chronic UVA-Exposed Dermal Fibroblasts	RP: Created a co-culture system and demonstrated that UVA irradiation increased oxidative stress. Confirmed a bystander transmission of reactive oxygen species from the fibroblast target to neighboring non-irradiated cells. MR: Melanoma and other skin cancers represent a significant disease burden to the U.S. military. Military personnel are at risk for higher UV radiation exposures and melanoma development and other skin cancers.	*Publication: 1*
CA093616 $659,431 Closed	Kemp/ Fred Hutchinson Cancer Research Center	Transgenerational Radiation Epigenetics	RP: Study to identify an epigenetic signature of radiation exposure in normal lung tissue and determine if these epigenetic changes are also seen in radiation-induced lung tumors. Showed that *in utero* irradiation leads to reduced body weight in young adult mice, which is transmitted through the maternal line to a subsequent generation. Also showed that *in utero* irradiation leads to increased incidence of lung tumors in susceptible mice. MR: Military personnel are at risk for radiation exposures (UV and gamma) and development of cancers.	*None*

Log Number/ Amount/ Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Genetic Cancer				
CA100459/P1 $1,204,447 Pending Closeout	Moritz; Foltz (Cobbs)/ Institute for Systems Biology, Swedish Health Services	Development of Advanced Technologies for Complete Genomic and Proteomic Characterization of Quantized Human Tumor Cells	RP: Study of three innovative new tools to find relevant biomarkers for novel approaches to the study of all cancers; technical development of whole genome sequencing and quantitative assays. Generated Glioblastoma cell lines from resected human tumor samples to allow for the study of cell type differentiation to define new molecular targets. Completed whole genome sequencing for two Glioblastoma patients and their families. Also completed the proteomic characterization of tumor development to establish diagnostic signature panels. MR: Technological advances supported by the military increase the ability of military medicine to answer the needs of Service members and their families.	*Publications: 4*
CA100545 $571,819 Closed	Broome/ Medical University of South Carolina	Targeting Cancer Protein Profiles with Split-Enzyme Reporter Fragments to Achieve Chemical Resolution for Molecular Imaging	RP: Study to advance imaging technology toward chemical resolution at the single cell level. A NIRF-EGF peptide probe was synthesized with a high affinity for EGFR and specific accumulation in cells overexpressing EGFR. Validated that the uptake of an EGFR targeted-complex in an orthotopic mouse brain tumor model correlated with upregulated EGFR expression. MR: Technological advances supported by the military increase the ability of military medicine to answer the needs of Service members and their families.	*Publications: 2* *Presentations: 23*

Log Number/ Amount/ Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Genetic Cancer				
CA120215 $417,501 Pending Closeout	Gutierrez/ Children's Hospital, Boston	Zebrafish Functional Genetics Approach to the Pathogenesis of Well-Differentiated Liposarcoma	RP: Examined oncogenes that contribute to well-differentiated liposarcoma in a zebra fish model. The PI found that FRS2 knockdown, not the hypothesized overexpression, promotes proliferation. Other results showed that expression of CDK4 or HMGA2 in zebra fish led to tumor formation. MR: Exposure to herbicidal agents and radiation predispose one to soft-tissue sarcomas. Development of effective therapies for sarcoma will benefit military Service members and Veterans.	*Presentations: 2*
Kidney Cancer				
CA100587 $454,900 Closed	Singamaneni/ Washington University	Label-Free, Point-of-Service Assay for Noninvasive Detection of Kidney Cancer	RP: Study to develop a urine test for kidney cancer. Demonstrated that a 3D surface enhanced Raman scattering substrate was 2 orders of magnitude more sensitive as compared to planar 2D substrate. Also demonstrated that the detection limit of AQP1, a urinary biomarker for kidney cancer, is 10 ng/ml. Created a novel biosensing platform in the form of bioplasmonic paper with a detection capability of 20 ng/ml for model bioanalytes. Developed an approach called bioplasmonic calligraphy to write biofunctionalized nanostructures on paper substrates. MR: Successful development of such a test will enable early cancer detection, removal at a curative and kidney-sparing stage, prompt recovery, and earlier return to active duty.	*Publications: 15* *Presentations: 12* *Funding obtained: 1 (NIH R21)*

Log Number/ Amount/ Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Kidney Cancer				
CA101070 $115,875 Closed	Wang/ University of California, San Francisco	Noninvasive Assessment of Renal Tumor Aggressiveness Using Hyperpolarized 13C MR	RP: Development of imaging tools to discriminate between indolent and aggressive renal cancers (RC). Demonstrated the feasibility of using ^{13}C pyruvate magnetic resonance to differentiate metastatic RC from localized RC. Renal cancer cell lines were metabolically characterized to study aggressiveness by evaluating their lactate and pyruvate flux. The study showed that metastatic RC cells have an increased export of hyperpolarized lactate to the extracellular space as compared to localized cells, suggesting that lactate production and export assessment using clinically translatable hyperpolarized probes could serve as a noninvasive tool in characterizing renal tumor aggressiveness. MR: Successful development of such a test will enable early cancer detection, removal at a curative and kidney-sparing stage, prompt recovery, and earlier return to active duty.	*Publication: 1* *Funding obtained: 2 (including a PRCRP Visionary Postdoctoral Award [CA110032 - Sriram])*
CA110032 $240,000 Pending Closeout	Sriram/ University of California, San Francisco	Hyperpolarized ^{13}C MR Markers of Renal Tumor Aggressiveness	RP: Established model systems of renal cell carcinoma (RCC) to study tumor metabolism using hyperpolarized carbon magnetic resonance. Demonstrated that there is increased lactate production in renal tumors and increased lactate efflux in aggressive renal cancers. MR: This work is of potential significant impact on military beneficiaries because of (1) the higher incidence of renal cell carcinoma in men versus women (2:1 ratio), (2) the risk of cigarette smoking (doubles the risk of renal cell carcinoma), and (3) the risk of occupational exposure to heavy metals, chlorinated solvents, and petrochemicals.	*Publications: 3* *Presentations: 5*

Log Number/ Amount/ Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Kidney Cancer				
CA110769 $296,000 Pending Closeout	Frisch/ West Virginia University	Role of Grainyhead in Kidney Cancer	RP: To study Grainyhead-like-2 (GRHL2), a transcription factor involved in kidney development, to determine its role as a tumor suppressor for renal cell carcinoma and how it prevents RCC progression. Results suggest that GRHL2 expression is highly protective against clear cell RCC by acting as a suppressor of the transcriptional activation function of p300, a protein required for oncogenic epithelial-mesenchymal transition. MR: Successful development of such a test will enable early cancer detection, removal at a curative and kidney-sparing stage, prompt recovery, and earlier return to active duty.	*None*
CA120409 $381,807 Pending Closeout	Shen/ Health Research, Inc., Roswell Park Division	A Novel Tumor Antigen and Foxp3 Dual-Targeting Tumor Cell Vaccine Enhances the Immunotherapy in a Murine Model of Renal Cell Carcinoma	RP: Characterization of the biological activity and therapeutic potential of a novel tumor cell antigen and Foxp3 dual-targeting in a RCC mouse model. Initial results indicate that tumor cell vaccines can successfully prevent tumor growth from an aggressive orthotopic RCC mouse model. MR: Service members have higher risk to develop kidney cancer because of deployment-related exposure to environment hazards.	*Presentation: 1* *Employment: 1 (The PI was promoted from postdoctoral fellow to Assistant Professor)*

Log Number/ Amount/ Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Listeria Vaccines				
CA100463 $543,200 Pending Closeout	Chung/ Memorial Sloan Kettering Cancer Center	Evaluation of Immune Responses Mediated by Listeria-Stimulated Human Dendritic Cells: Implications for Cancer Vaccine Therapy	RP: The study demonstrated that *Listeria* infection induced monocyte-derived dendritic cell (moDC), dendritic cell (DCs), and Langerhans cell maturation and activation, leading to T-cell proliferation. These findings confirmed that *Listeria* could stimulate an immune response and potentially serve as a DC vaccine adjuvant. Findings also support the role of Listeria in augmenting the immunity of moDCs, the most commonly used DC in clinical trials, to optimize DC-based cancer vaccines. MR: The development of immune-enhanced technology will benefit military medicine from cancer to infectious diseases (a main exposure risk in deployed military populations).	*Publication: 1*
CA110297 $296,000 Pending Closeout	Bahjat/ Providence Portland Medical Center	Synergy of SOCS-1 Inhibition and Microbial-Based Cancer Vaccines	RP: To test that the induction of negative regulators of inflammation and cytokine signaling, such as SOCS-1, limit the potency of the tumor-specific immune response and that the inhibition of SOCS-1 will enhance the anti-tumor efficacy of a *Listeria monocytogenes*-based cancer vaccine. Demonstrated that targeting SOCS1 function in infected cells does improve the magnitude of elicited T-cell responses. MR: Melanoma has been shown to be an immunogenic malignancy, whose incidence has tripled within the last two decades. U.S. troop deployment to areas with intense daily sun exposure will unfortunately increase the risk of melanoma in these Soldiers. The development of a next-generation vaccine for the treatment of malignant melanoma should therefore be of interest to the military.	*None*

Log Number/ Amount/ Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Melanoma/Skin Cancer				
CA093471/P1 $1,187,984 Closed	Hernando; Osman/ New York University School of Medicine	Altered microRNAs in Melanoma Brain Metastasis	RP: Demonstrated the addition of miRNA expression signature to the current staging criteria improves the ability to predict the development of brain metastasis; it improves the melanoma clinical management; identified two miRNA whose loss promotes metastasis; and identified one miRNA suppresses metastasis. MR: The prevention, detection, and treatment of melanoma are of particular importance to the military population, who are at high risk due to the deployment-related exposure to UV radiation.	*Publications: 5* *Presentations: 3* *Patent: 1* *Funding obtained: 1*
CA093473/P1 $1,196,001 Closed	Halaban; Brash; Bosenberg/ Yale University	UVL, ROS, Pigmentation, Genetic Predisposition, and Epigenetic Gene Silencing in Melanoma	RP: Study of the linkage between reactive oxygen species, genetic and epigenetic changes, and UV radiation leading to melanoma development. Found a "photochemistry in the dark" phenomenon: DNA damage by UV light continued after sun exposure. MR: The prevention, detection, and treatment of melanoma are of particular importance to the military population, who are at high risk due to the deployment-related exposure to UV radiation.	*Publications: 5* *Patent: 1*
CA100039 $561,626 Pending Closeout	Antony/ University of Maryland, Baltimore	Mechanisms of Relapsing Cancer and the Origin of Melanoma-Specific Regulatory T Cells	RP: Study of immunosuppression and melanoma development. Found a more complexed role of T_{reg} cells in melanoma relapse. Showed that T_{reg} cells prevent treatment of relapse and also that T effector cells become exhausted and can be rescued by antibody therapies to chronic inhibitory receptors. MR: The high exposure to UV radiation to military personnel during deployment is associated with increased risk for melanoma.	*Publication: 1* *Funding obtained: 1*

Log Number/ Amount/ Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Melanoma/Skin Cancer				
CA100311 $581,250 Closed	Aplin/ Jefferson Medical College	Role and Regulation of FOXD3 in Mutant B-RAF Melanoma	RP: Established systems to analyze the response of melanoma xenografts to RAF inhibitors in vivo and showed the downregulation of FOXD3 targets enhances the effects of RAF inhibitors in vivo. Data also indicate that ERBB3 signaling is important in the response to RAF inhibitors both in vitro and in vivo. MR: The prevention, detection, and treatment of melanoma are of particular importance to the military population, who are at high risk due to the deployment-related exposure to UV radiation.	*Publications: 2* *Presentations: 6* *Funding obtained: 1 (NIH R01)*
CA101019 $116,250 Closed	Aplin/ Jefferson Medical College	Novel Mechanisms of Resistance to B-RAF Inhibitors in Melanoma	RP: Study into the novel mechanisms of chemotherapy resistance to RAF inhibitors and melanoma treatments. Developed a system to quantify changes in ERK1/2 signaling in tumor cells with elevated activity and showed that mutant NRAS is sufficient to confer resistance to RAF inhibitors and that mutant NRAS-resistant cells alter their signaling connections in response to RAF inhibitor. MR: The rate of new melanoma diagnoses among Service members is higher than that of the general population even after correcting for age and ethnicity.	*Publication: 1* *Patent: 1*

Log Number/ Amount/ Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Melanoma/Skin Cancer				
CA101118 $114,750 Closed	Serafini/ University of Miami School of Medicine	Converting Myeloid-Derived Suppressor Cells into Immunogenic Antigen-Presenting Cells in Melanoma-Bearing Mice	RP: Investigation of the conversion of the tolerogenic myeloid-derived suppressor cells by siRNA into functional immunogenic activated protein C to generate effective tumor immunity. Confirmed genetic modification via shRNA of tumor-educated myeloid cells alters the immune system by creating an anti-tumor immune response able to restrain the growth of melanomas. Developed an IL4-PAMAM dendrimer platform able to target tumor-educated myeloid cells and myeloid-derived suppressor cells in vivo. MR: Service members are deployed to areas of high risk and exposure to UV light. With more and more deployment of troops in countries with high sun exposure and UVA and UVB penetration (e.g., Afghanistan, Iraq, and the Middle East region), melanoma can be the most frequent cancer that military personnel will face during their lives.	*Presentation: 1* *Funding obtained: 1 (BCRP Idea Award)*
CA101202 $130,498 Closed	Libermann/ Beth Israel Deaconess Medical Center, Boston	Testing New Drugs for Treatment of Melanoma Patients Applying Connectivity Map Database Analysis with Melanoma Gene Signatures	RP: To identify drugs for treating metastatic melanoma through the use of meta-analysis of melanoma transcriptome data to generate a metastatic melanoma gene signature. This gene signature was then applied to the Connectivity Map Database of drug gene signatures. By using this strategy, several drugs were identified that are strong inducers of apoptosis in melanoma cell lines. MR: Military personnel are at risk for UV radiation exposures and development of cancers.	*None*

Log Number/ Amount/ Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Melanoma/Skin Cancer				
CA110011 $240,000 Pending Closeout	Ransom/ University of Colorado, Denver	Determining the Location of DNA Modification and Mutation Caused by UVB Light in Skin Cancer	RP: To map and characterize UVB damaged "hotspots" in the human genome using a novel enzyme and sequencing methodology. This study optimized a new ligation-based method to study DNA modification caused by UV exposure and found that known regulatory domains within the genome, promoters and enhancers are more susceptible to UV damage. MR: Service members are deployed to areas of high risk and exposure to UV light. With more and more deployment of troops in countries with high sun exposure and UVA and UVB penetration (e.g., Afghanistan, Iraq, and the Middle East region), melanoma can be the most frequent cancer that military personnel will face during their lives.	*Publication: 1* *Presentations: 2*
CA110017 $368,400 Pending Closeout	Goding/ University of Maryland, Baltimore	Therapeutic Intervention for the Treatment of Relapsing Melanoma	RP: To determine the roles of chronic CD4 T-cell exhaustion and the inhibitory pathways involved in melanoma tumor relapse. CD4+T cells from mice with relapsing tumors expressed hallmark indicators of chronic exhaustion, and when the mice were treated for exhaustion, tumors regressed and the markers decreased. MR: The rate of new melanoma diagnoses among Service members is higher than that of the general population even after correcting for age and ethnicity. Melanoma is strikingly the second most common cancer among males in the U.S. Navy. Military personnel are at risk for UV radiation exposures and development of cancers.	*Publications: 2* *Presentations: 2*

Log Number/ Amount/ Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Melanoma/Skin Cancer				
CA110107 $259,200 Closed	Zhang/ Mount Sinai School of Medicine	Insight into Skin Tumorigenesis Highlighting the Function of Epigenetic Regulators in SCC Formation	RP: To dissect the Ezh2 regulatory network that controls skin squamous cell carcinoma (sSCC) formation, focusing on the evaluation of regulatory networks and their mechanisms in control of the early steps of sSCC formation. Observations suggest that Ezh2 may function in multiple ways to form a regulatory network and imply a new and unexpected H3K27me3-independent mechanism. MR: Service members are deployed to areas of high risk and exposure to UV light.	*Publication: 1* *Award ended early due to the PI being offered a faculty position at the Qingdao University of Science and Technology (China)*
CA110183 $313,000 Pending Closeout	Marchetti/ Baylor College of Medicine	Heparanase Mechanisms in Melanoma Brain Metastasis	RP: To examine the use of heparanase as a novel therapeutic target for the personalized treatment of melanoma brain metastasis (MBM). This study identified SST001 as an anti-heparanase compound that inhibits MBM tumor growth in vivo and established that heparanase activity is a molecular determinant of BMM onset that can be mitigated by treatment with SST001. MR: Malignant melanoma, associated with increased sun exposure, is a cancer type with the most aggressive propensity to colonize the brain. Better understanding of the mechanism of metastasis will lead to treatments that will improve quality of life for those prone to this type of cancer including active military.	*Publication: 1*

Log Number/ Amount/ Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Melanoma/Skin Cancer				
CA110338 $296,400 Closed	Bikle/ Northern California Institute for Research and Education	The Tumor Suppressor Actions of the Vitamin D Receptor in Skin	RP: Developed mouse models for the expression of the hedgehog and wnt/beta-catenin pathways to determine if they would alter the susceptibility of the VDR null mouse to UVB-induced epidermal cancer. Conducted short UVB exposure studies for most of the developed mouse models. MR: The rate of new melanoma diagnoses among Service members is higher than that of the general population even after correcting for age and ethnicity. Military personnel are at risk for UV radiation exposures and development of cancers.	*Publications: 7* *Presentation: 1*
CA110396 $327,333 Pending Closeout	Faller/ Boston University Medical Campus	Targeting N-Ras as a Therapeutic Approach for Melanoma	RP: To test whether the inhibition or downregulation of PKCδ in human and murine models of melanoma with aberrant activation of N-RAS signaling will cause targeted cytotoxicity in melanoma tumors. Results validate PKCδ as a target and provide proof of principle for the use of PKCδ inhibitors as a strategy to eliminate BRAF mutant melanomas resistant to BRAF inhibitors. MR: Service members are deployed to areas of high risk and exposure to UV light.	*Publications: 3* *Presentation: 1*
CA110462 $289,871 Pending Closeout	Zhang/ University of Colorado, Denver, Anschutz Medical Campus	Targeting "Dynamic Stemness" of Melanoma by Blocking the NADH-Dependent CtBP Function	RP: To study whether hypoxia, hyperglycemia, and UV irradiation trigger the conversion of melanoma cells by the activation of CtBP-mediated transcription and if blocking its function can be used as a novel therapeutic strategy. Found that CtBP hyperfunction leads to the induction of the H3K4 demethylase JARID1B protein, a key marker for melanoma self-renewal. Determined that NADH rise induced by hypoxia upregulates JARID1b mRNA levels in melanoma cells. MR: Military personnel are at risk for UV radiation exposures and development of cancers.	*Publication: 1*

Log Number/ Amount/ Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Melanoma/Skin Cancer				
CA110602 $284,597 Pending Closeout	Hernando/ New York University School of Medicine	Identification of Glycomic Alterations during Melanoma Metastasis	RP: To better understand the changes that occur within the tumor microenvironment that may be triggered by microRNAs released from melanoma cells with specific interest in the sugars present on the surface of cells. Data suggest that microRNA linked alterations in cell surface sugars may be an early event in the malignant transformation of melanocytes to melanoma. MR: Deployment to areas of high UV exposures puts Service members at increased risk for the development of melanoma and other skin cancers. This study directly relates to military population and risk.	*Publications: 3* *Presentation: 1*
CA110802 $305,000 Pending Closeout	Morris/ University of Minnesota, Twin Cities	A Novel Mechanism for the Pathogenesis of Nonmelanoma Skin Cancer Resulting from Early Exposure to Ultraviolet Light	RP: To examine whether stem cells that reside within the skin can be provoked in to migrating to other tissues upon UV irradiation. Findings support the hypothesis that skin keratinocytes can leave the cutaneous epithelium and enter the blood and bone marrow. Results indicate that the bone marrow may act as a long-lived reservoir of these UV-damaged cells that may be used to repopulate the skin years after damage has occurred. MR: The rate of new melanoma diagnoses among Service members is higher than that of the general population even after correcting for age and ethnicity.	*Presentations: 1*
CA110823 $308,000 Pending Closeout	Bullock/ University of Virginia	Functional Proteomics to Identify Moderators of CD8+ T-Cell Function in Melanoma	RP: This study uses the technique of phage-display to express a library of proteins with the intention of identifying new binding partners of tumor-infiltrating (TIL) T cells. Identified 17 unique agents that selectively bind TIL T cells without cross-reactivity with other lymphocytes. These can be used as new tools for T-cell identification and tumor visualization. MR: Military at risk for UV radiation exposures and development of cancers.	*Presentations: s3*

Log Number/ Amount/ Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Melanoma/Skin Cancer				
CA111032 $305,000 Pending Closeout	Basu/ Ohio State University	Role of Catecholamines in the Regulation of Angiogenesis in Preneoplastic Skin Lesions	RP: A study aimed at determining the role of dopamine receptors and adrenoceptors in skin carcinogenesis. Developed a mouse model of skin carcinogenesis and demonstrated that vascular endothelial growth factor (VEGF)-induced angiogenesis is responsible for the initiation and progression of the disease model. Furthermore, blocking the synthesis of VEGF by treatment with dopamine receptor or adrenoceptor modulators reduced tumor number as well as tumor size in these animals. MR: Service members are deployed to areas of high risk and exposure to UV light.	*Presentations: 7*
CA120161 $417,600 Pending Closeout	Wu/ Massachusetts General Hospital	Targeting Palmitoyl Acyltransferases in Mutant NRAS-Driven Melanoma	RP: Development of a new class of palmitoyl acyltransferase inhibitors (PATs) that target N-RAS mutant melanomas. These potent chemical probes were used to identify all PATs expressed in melanoma cells MR: Treatment of melanoma may be of importance to military populations, as military service often requires prolonged outdoor activity resulting in high exposure to ultraviolet light, the leading risk factor for melanoma.	*Publications: 2* *Funding obtained: 2*
CA120240 $399,600 Pending	Yan/ Yale University	Targeting Epigenetic Regulator JARID1B in Malignant Melanoma	RP: Determination of the effects after the loss of an epigenetic regulator, JARID1B, on melanoma formation and progression. Found that mitochondrial transcription as well as WNT and mTOR signaling are modified in the absence of JARID1B leading to decreased cell proliferation in melanoma cells. Results have shown that loss of JARID1B delays tumor formation and treatment with newly developed protein specific inhibitors decreases cancer cell colony formation. MR: Melanoma can be caused by heavy sunlight exposure, such as for Service members in areas like Iraq. Identification of new drug therapies will have significant impact on treatments for those at higher risk of this cancer.	*Publications: 2* *Presentations: 24* *Funding obtained: 2* *The PI was promoted to Associate Professor on 1 July 2014*

Log Number/ Amount/ Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Mesothelioma				
CA110442 $296,850 Closed	Robinson/ University of Western Australia	Targeting Immunological Restrainers: Understanding the Immunology behind Combination Chemoimmunotherapy to Improve the Treatment of Malignant Mesothelioma	RP: To determine if the adaptive immune response plays a key role in the early changes associated with mesothelial cell transformation and tumor development and is inhibited by immunological restraints. Observed that the depletion of Treg cells can significantly enhance anti-tumor immunity and delay tumor development. Also found that targeted Treg removal in combination with gemcitabine chemotherapy significantly enhanced overall survival in comparison to chemotherapy alone. Observed that asbestos induced mesothelioma development is slower in mice that lack a functional immune system compared to mice that are immune competent. MR: Initial exposure to the diagnosis of the disease. Long-term risk of mesothelioma development following asbestos exposures is critical for U.S. Veterans and active military.	*None*
CA110765 $316,000 Pending Closeout	Salgia/ University of Chicago	PI3K as a Therapeutic Target in Malignant Pleural Mesothelioma	RP: To investigate the therapeutic potential of phosphatidyl inositol 3'-kinase (PI3K) in malignant pleural mesothelioma (MPM) and determine the efficacy of some of the PI3K and PI3K/TOR inhibitors in MPM cell culture and mouse models. Results suggest that a combination of drugs is more effective than using each alone in suppressing tumor growth and motility. MR: Asbestos exposure was widespread among Naval personnel even after the 1980s. Long-term risk of mesothelioma development following asbestos exposures is critical for U.S. Veterans and active military.	*Publication: 1* *Presentation: 1*

Log Number/ Amount/ Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Mesothelioma				
CA110772 $294,870 Pending Closeout	Heasley/ University of Colorado, Denver, Anschutz Medical Campus	Targeting Fibroblast Growth Factor Receptor Signaling Pathways in Mesothelioma	RP: To test the hypothesis that the co-expression of fibroblast growth factors (FGFs) and FGF receptors create an autocrine growth loop in mesothelioma that promotes cancer growth. Studies support that FGFR1 activation through autocrine FGF2 is a driver of oncogenic growth in a subset of mesothelioma cell lines. Determined that FGFR1 is a novel target for therapeutic intervention in mesothelioma. MR: Long-term risk of mesothelioma development following asbestos exposures is critical for U.S. Veterans and active military.	*Publication: 1*
Non-Invasive Ablation Only				
CA093108 $114,836 Closed	O'Donnell/ University of California, Davis	Immuno-Nanomicelles Targeted Therapy of Non-Hodgkin's Lymphoma	RP: Research into fabrication and development of nanomicelles for the direct delivery of treatment (chemotherapy) to a disease site (non-Hodgkin's lymphoma). Developed immuno-nanomicelles to specifically target tumors and increase the therapeutic index of chemotherapy. Mice treated with encapsulated micelles had a superior anti-tumor response as compared to using vincristine alone. MR: Biomedical development of nanotechnology that is translatable to various treatments for diseases, conditions, and injuries specific to the military deployments and exposure risks, e.g., Agent Orange.	*Publications: 2*
CA093166 $134,884 Closed	Gach/ Nevada Cancer Institute	Targeted RF Ablation of Tumors Using Monocyte/Macrophage Carriers of Conductive Nanoparticles	RP: Development of radiofrequency (RF) ablation therapies for specific treatment of tumors. Observed that metallic single-wall carbon nanotubes may have the potential to generate enough heat at biologically relevant concentrations to have an impact in clinical use. MR: Development of a new treatment modality for tumor ablation may translate to expansive medical methodologies with military benefit.	*Publications: 2* *Presentation: 1*

Log Number/ Amount/ Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Non-Invasive Ablation Only				
CA093180 $117,684 Closed	Berdis/ Case Western Reserve University	Gold-Containing Nucleosides as Noninvasive Ablation Agents	RP: Development of gold-containing nucleosides as target agents to potentiate the efficacy of ionizing radiation for maximal tumor ablation. Results positively highlighted the applicability of combining Au(I)-indoles with ionizing radiation as a new strategy to ablate tumors using non-invasive techniques. MR: Technological advances supported by the military increase the ability of military medicine to answer the needs of Service members and their families.	*Publication: 1*
CA093210 $117,000 Closed	Pan/ University of Chicago	Testing Delivery Platforms for New Anticancer tRNA-Based Drugs	RP: Development of killer tRNA nanoparticles as a potential blood cancer treatment. Obtained proof of concept results in blood cancer cells encouraging the continued development of efficient delivery systems. MR: The military benefits through the development of drug delivery systems to decrease side effects and increase efficacy. Technology can be broadly employed for various treatments outside cancer.	*None*
CA093389 $598,307 Closed	Torti/ University of Connecticut	Targeted Nanoparticles for Kidney Cancer Therapy	RP: Development of novel optically activated multifunctional nanotubes to target and kill renal cancer cells. Soluble D5-conjugated nanotubes were produced; the toxicity of unconjugated nanotubes to kidney cancer cells was tested. The results demonstrated that the combination of NIR and nanotubes could successfully inhibit both human and mouse kidney cancer cells. MR: Biomedical development of nanotechnology that is translatable to various treatments for diseases, conditions, and injuries specific to the military will benefit military personnel.	*Publications: 4* *Presentation: 2*

Log Number/ Amount/ Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Non-Invasive Ablation Only				
CA093453 $670,720 Closed	Panyam/ University of Minnesota, Twin Cities	Targeted Magnetic Hyperthermia for Lung Cancer	RP: The study demonstrated that super paramagnetic iron oxide nanoparticles with EGFR targeting ligand enhanced tumor cell uptake and in vivo mouse lung retention. MR: Military biomedical development of nanotechnology that is translatable to various treatments for diseases, conditions, and injuries specific to the military will benefit military personnel.	*Publications: 4* *Presentations: 15*
Pancreatic Cancer				
CA110076 $368,400 Pending Closeout	Lunt/ Michigan State University	Understanding the Warburg Effect and the Metabolic Requirements of Cancer Cells	RP: The PI studied the role of pyruvate kinase (PK) isoform expression in altered metabolism in pancreatic and blood cancer cells. She created cell lines that express different isoforms of PK and mass spectrometry based methods to study them. Using these tools, the PI was able to elucidate the mechanism by which the isoform PKM2 deletion leads to proliferation arrest in normal cells. MR: Higher risk of pancreatic cancer has been shown in populations exposed to pesticides such as Agent Orange. Higher risk of pancreatic cancer in Vietnam nurses has been reported.	*Publications: 5* *Presentations: 8* *Funding obtained: 2 (one from CDMRP's BCRP)* *Employment: 1 (The PI was promoted from postdoctoral fellow to Assistant Professor as the close of this award.)*
CA110164 $296,000 Closed	Houchen/ University of Oklahoma Health Sciences Center	Tuft Cell Regulation of miRNAs in Pancreatic Cancer	RP: The PI tested the hypothesis that tuft cells are specialized chemosensing cells in the pancreas, and that with the appropriate oncogenic signals tuft cells may become the cells of origin for pancreatic cancer. Progress to date includes the successful deletion of DclK1 throughout the pancreatic ducts of a transgenic mouse model. MR: Higher risk of pancreatic cancer has been shown in populations exposed to pesticides such as Agent Orange. Higher risk of pancreatic cancer in Vietnam nurses has been reported.	*Publication: 1* *Presentation: 1* *Funding obtained: 1 (NIH R01)*

Log Number/ Amount/ Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Pancreatic Cancer				
CA110449 $320,000 Closed	Beatty/ University of Pennsylvania	Listeria Vaccines for Pancreatic Cancer	RP: Examination of whether *Listeria* vaccines can overcome the immune suppression associated with pancreatic ductal adenocarcinoma by stimulating anti-tumor responses able to target both tumor cells and their surrounding microenvironment. Found that *Listeria* vaccines produce little impact on late-stage tumors with an absence of T-cell infiltration into tumor tissue, but do appear to have non-antigen specific anti-stromal effects. MR: Higher risk of pancreatic cancer has been shown in populations exposed to pesticides such as Agent Orange. Higher risk of pancreatic cancer in Vietnam nurses has been reported.	*Publications: 4* *Presentations: 2* *Patent: 1 (provisional)*
CA110530 $241,880 Pending Closeout	Solomon/ National Cancer Institute	Metabolomic Profiles and Pancreatic Cancer Risk	RP: The study of metabolites to identify those associated with pancreatic cancer to define profiles correlating with risk levels. Metabolites have been measured on fasting serum samples and preliminary analysis has been conducted. MR: Higher risk of pancreatic cancer has been shown in populations exposed to environmental agents and pesticides such as Agent Orange. Higher risk of pancreatic cancer in Vietnam nurses has been reported.	*None*
CA110535 $310,000 Pending Closeout	Yu/ Emory University	The Replication Stress Response in Pancreatic Cancer	RP: To identify Replication Stress Response genes and evaluate them as potential biomarkers for pancreatic cancer treatment response. Completed a loss of function genetic screen using a siRNA library of somatically mutated genes. Selected 20 gene candidates for further analysis to determine their activities in DNA replication and damage responses. MR: Higher risk of pancreatic cancer has been shown in populations exposed to environmental agents and pesticides such as Agent Orange.	*Publications: 3* *Presentations: 25* *Funding obtained: 1 (NIH R01)*

Log Number/ Amount/ Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Pancreatic Cancer				
CA110636 $313,690 Closed	Fletterick/ University of California, San Francisco	Inhibition of Pancreatic Cancer Cell Proliferation by LRH-1 Inhibitors	RP: To find selective and potent compounds that inhibit LRH-1 activity in human pancreatic ductal adenocarcinoma cells (PDAC). Performed computational filtering of over 5 million compounds. Demonstrated that PDAC cells expressing LRH-1 are sensitive to treatments with receptor specific inhibitors and that growth and proliferation of LRH-1 positive cancer cells could be markedly decreased following such treatments. Sent two compounds to the National Cancer Institute Chemotherapeutic Agents Repository for use in the research community. MR: Higher risk of pancreatic cancer has been shown in populations exposed to environmental agents and pesticides such as Agent Orange.	*Publications: 2* *Presentations: 2*
CA110724 $289,988 Pending Closeout	Phanstiel/ University of Central Florida	Development of Novel Cancer Therapies that Target Polyamine Metabolism	RP: To determine if sustained polyamine depletion in human pancreatic cells leads to apoptosis so that a combination therapy can be developed using inhibitors of polyamine biosynthesis and transport. Identified a new gene associated with polyamine transport that could serve as a potential biomarker. Combination therapy of new polyamine inhibitors showed efficacy in pancreatic cancer mouse models. MR: Higher risk of pancreatic cancer has been shown in populations exposed to environmental agents and pesticides such as Agent Orange.	*Publications: 5* *Patent: 1 (applied for)* *Presentations: 15*

Log Number/ Amount/ Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Pancreatic Cancer				
CA110731 $340,894 Closed	Corcoran/ Massachusetts General Hospital	An in Vivo shRNA-Drug Screen to Identify Novel Targeted Therapy Combinations for KRAS Mutant Cancers	RP: To use a novel in vivo RNAi drug screening approach to rapidly identify genes that, when inhibited, allow MEK inhibitors to work against KRAS mutant pancreatic cancer cells. Completed the primary in vitro shRNA drug screen and prioritized the top 100 gene targets for a secondary screen in an orthotopic mouse model of pancreatic cancer. MR: Higher risk of pancreatic cancer has been shown in populations exposed to environmental agents and pesticides such as Agent Orange.	*None*
CA110832 $290,720 Pending Closeout	Mukherjee/ University of North Carolina, Charlotte	A Novel Association and Therapeutic Targeting of Neuropilin-1 and MUC1 in Pancreatic Cancer	RP: Exploration of the hypothesis that MUC1, a marker of aggressive tumors, is driving metastatic spread by increasing Neurophilin 1 levels within pancreatic tumors. Showed that NRP1 may be an excellent target for treating MUC1-positive, but not negative, pancreatic ductal adenocarcinoma. Developed a novel antibody-anti-angiogenic drug conjugate. MR: Higher risk of pancreatic cancer has been shown in populations exposed to environmental agents and pesticides such as Agent Orange.	*Publications: 1* *Presentations: 1*
CA110994 $388,633 Closed	Sabatini/ Whitehead Institute for Biomedical Research	Targeting Pathways that Process Endogenous Toxic Metabolites in Pancreatic Cancers	RP: To identify the pathways that produce and remove endogenous toxic metabolites in pancreatic cancers and to examine how those pathways can be targeted to selectively cause toxicity in pancreatic cancer cells. Results suggest that intermediates of tryptophan breakdown may be good targets for therapies based upon toxic metabolites. MR: Higher risk of pancreatic cancer has been shown in populations exposed to environmental agents and pesticides such as Agent Orange.	*None*

Log Number/ Amount/ Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Pancreatic Cancer				
CA111019 $311,152 Closed	Jacks/ Massachusetts Institute of Technology	Investigating the Mechanism of K-RAS-Independent Growth of Murine Pancreatic Ductal Adenocarcinoma in Vitro and in Vivo	RP: To use RNAi-based technology to knock down K-RAS mutant cells both in vivo and in vitro to identify the K-RAS-independent growth pathways in pancreatic cancer that can be targeted for drug therapy. Progress includes the identification and characterization of a reversible K-ras-independent state as murine cells, both in vitro and in vivo, can survive and proliferate despite persistent K-ras knockdown. MR: Higher risk of pancreatic cancer has been shown in populations exposed to environmental agents and pesticides such as Agent Orange.	*Presentation: 1* *Funding obtained: 1*
CA111036 $215,325 Closed	Kimmelman/ Dana-Farber Cancer Institute	In Vivo Measurement of Oncogenic Kras-Dependent Glucose Metabolism in Mouse Models of Pancreatic Cancer	RP: To develop a novel method to measure the incorporation of glucose into pancreatic tumor models to assess where it is metabolized to develop a list of critical elevated metabolites and their associated pathways. Using a mouse model of pancreatic cancer, the PI refined methods to label tumors in vivo using ^{13}C glucose. MR: Higher risk of pancreatic cancer has been shown in populations exposed to environmental agents and pesticides such as Agent Orange.	*Publication: 1*
CA120057 $410,940 Pending Closeout	Ting/ Massachusetts General Hospital	Impact of Noncoding Satellite Repeats on Pancreatic Cancer Metastasis	RP: To study the role of RNA satellites in pancreatic cancer genetics, metastasis, and circulating tumor cells. Assessed HSATII in pancreatic circulating tumor cells (CTCs) with results suggesting it as a blood-based early detection biomarker. MR: Higher risk of pancreatic cancer has been shown in populations exposed to environmental agents and pesticides such as Agent Orange. Higher risk of pancreatic cancer in Vietnam nurses has been reported.	*Publications: 2* *Patents: 1 (applied for)* *Presentations: 5* *Funding obtained: 2 (PanCAN, ACS)*

Log Number/ Amount/ Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Pancreatic Cancer				
CA120188 $373,200 Pending Closeout	Rhim/ University of Michigan	A Novel Mechanism for Post-Transcriptional Regulation in Pancreatic Cancer Progression	RP: To study the RNA-DNA differences (RDDs) in pancreatic pre-cancer and tumor cells and determine the genes in which RDDs occur during cancer progression. Using refined techniques to isolate high-quality RNA for sequencing, and developing a new bioinformatics platform to analyze the data, the PI found widespread RDDs in a mouse model of pancreatic cancer. MR: Pancreatic cancer is one of the most lethal forms of cancer that affects Service members, Veterans, and military beneficiaries and their families.	*Presentations: 15* *Funding obtained: 4 (including being a Co-I on an NIH R01)*
CA120412 $349,382 Pending Closeout	Nagrath/ University of Michigan, Ann Arbor	Integrated Microfluidic Magnetic CTC Sorter and Enumerator for Early Diagnosis and Management of Pancreatic Cancer	RP: The PI successfully development an integrated microfluidic magnetic cell sorter and enumerator to separate circulating tumor cells (CTCs) from the blood of pancreatic patients. The device could detect CTCs in 100% of patient samples, and the CTCs could be sorted to an average of 82.5% purity. The high purity level allowing for further testing and characterized of the patient samples, which supports the use of this devise in clinical trial design. MR: Higher risk of pancreatic cancer has been shown in populations exposed to environmental agents and pesticides such as Agent Orange.	*Publication: 1* *Presentations: 3* *Funding obtained: 1*
CA140580 $479,488 Early Termination	O'Bryan/ University of Illinois Chicago	Development of Novel Ras Inhibitory Agents for Cancer Therapy	RP: Develop engineered proteins (monobodies) that target specific KRas mutations commonly found in pancreatic cancer. Then test the efficacy of these monobodies in blocking the tumorigenic phenotype in KRas-mutant tumors. MR: Veterans have a five- to seven-fold increased incidence of Ras mutant cancers. Thus, any novel therapies that evolve from this research would greatly benefit military personnel and their families.	*None*

Log Number/ Amount/ Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Pediatric Brain Tumor				
CA093469/P1/P2/ P3 $1,786,229 Closed	Gilbertson; Guy; Ellison; Malkin/ St. Jude Children's Research Hospital; Hospital for Sick Children	Molecular-Targeted Therapies of Childhood Choroid Plexus Carcinoma (CPC)	RP: Large throughput screening to study candidate oncogenes and potential drug targets for rare cancers. Validated the overlapping human and mouse genetics and initiated the first whole genome sequencing of CPC. Screened 1.26 million compounds in the primary round and 688 compounds in the secondary round and identified 23 hits. The highest hit was gemcitabine, a Food and Drug Administration-approved drug. Selected five compounds for preclinical study and demonstrated in vivo efficacy and favorable pharmacology of gemcitabine that can be progressed immediately to clinical trial. MR: Development of cost-efficient screening techniques for rare diseases will benefit military medicine.	*Presentations: 10*
CA100157 $465,000 Closed	Read/ Emory University	Identification and Characterization of Metastatic Cancer Stem Cells in Medulloblastoma	RP: To identify and characterize cells responsible for metastatic disease in medulloblastoma patients, identify genetic markers that predict metastasis, and find novel molecular targets for therapeutics. Found that smo/smo and ptc +/- primary medulloblastoma could be propagated by CD15+/Math1+ cancer stem cells. Identified a unique protein, Math1, as well as markers and drivers of metastasis as therapeutic targets. MR: Epidemiology studies have shown that several forms of cancer including pediatric brain tumors have higher incidence in military populations compared to the general population. Environmental exposure to cytotoxic and chemical carcinogens could be a contributing factor.	*None*

Log Number/ Amount/ Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Pediatric Brain Tumor				
CA100335 $450,843 Closed	Keating/ University of Colorado, Denver, Anschutz Medical Campus	Targeting Pediatric Glioma with Apoptosis and Autophagy Manipulation	RP: Confirmed the upregulation of autophagy by Mer and Axl shRNA inhibition in several human glioma cell lines. Successful inhibition of Mer and Axl RTK with a commercially available small molecule inhibitor resulted in increased apoptosis, decreased migration, and suppressed tumor growth. Results suggest that Mer and Axl RTK signaling regulates autophagy pathway activation in glioma cells to determine the efficiency of glioma cell killing. MR: The health and welfare of the force is partially determined by the health and welfare of their supportive families. Military missions benefit when the Warfighters' families are healthy and well.	*Publications: 4* *Presentations: 3*
CA100469 $531,373 Pending Closeout	Zong/ University of Virginia	Social Behavior in Medulloblastoma: Functional Analysis of Tumor-Supporting Glial Cells	RP: Investigation for understanding the crosstalk between glial cells and medulloblastoma. The study found that glial-ablation treatment resulted in complete remission of tumors and such treatment was also effective for late-stage tumors. MR: The health and welfare of the force is partially determined by the health and welfare of their supportive families. Military missions benefit when the Warfighters' families are healthy and well.	*Presentations: 9*

Log Number/ Amount/ Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Pediatric Brain Tumor				
CA100601 $456,583 Closed	Becher/ Duke University	Genetically Engineered Mouse Model of Diffuse Intrinsic Pontine Glioma as a Preclinical Tool	RP: Development of valid animal models to promote understanding of tumorigenesis, safety, and toxicities of therapies and identification of novel therapeutic targets and/or resistance mechanisms. Generated several diffuse intrinsic pontine glioma mouse models. Identified the transcription factor, pax3, to be significantly upregulated in a diffuse intrinsic pontine glioma (DPIG) model, but not in a cortical glioma model, although both were driven by the same genetic alterations. MR: The health and welfare of the force is determined by the health and welfare of their supportive families. Military missions benefit when the Warfighters' families are healthy and well.	*Publications: 4* *Presentations: 2* *Funding obtained: 1*
CA100735 $511,136 Pending Closeout	Paddison/ Fred Hutchinson Cancer Research Center	Pediatric Glioblastoma Therapies Based on Patient-Derived Stem Cell Resources	RP: Isolation and characterization of glioma stem cells (GSC) from pediatric patients in orthotopic xenograft mouse models and the assessment of whether they diverge from adult GSC. The PI isolated and characterized several patient-derived cell lines through gene expression analysis and patient-specific gene mutations and has begun to identify candidate therapeutic targets. MR: The health and welfare of the force is partially determined by the health and welfare of their supportive families. Military missions benefit when the Warfighters' families are healthy and well.	*Publications: 4* *Patent: 1* *Presentations: 5* *Funding obtained: 1 (NIH R21)*

Log Number/ Amount/ Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Pediatric Brain Tumor				
CA101163 $117,975 Closed	Li/ Baylor College of Medicine	Harnessing Autopsied DIPG Tumor Tissues for Orthotopic Xenograft Model Development in the Brain Stems of SCID Mice	RP: Development of mouse models to better understand carcinogenesis and its treatment. Created two orthotopic xenograft models for DPIG via the engrafting of autopsy tumor cells into the brains of SCID mice. Demonstrated that xenograft tumors could replicate key histopathological features of the original tumor. MR: Advancing genetic research has a direct application to active, reserve, and retired U.S. military personnel and their families, as a military lifestyle entails potential exposure to carcinogens known and presumed, chemical and physical/radioactive in nature, both in training and in deployment, and related to equipment utilization and/or combat.	*Publication: 1 (Nature Medicine)* *Presentation: 1* *Funding obtained: 5 (including 1 NIH R01)*
CA130562 $372,600 Early Termination	Mulcahy Levy/ University of Colorado at Denver	Targeting BRAF V600E and Autophagy in Pediatric Brain Tumors	RP: Found that inhibiting autophagy enhance the activity of BRAF inhibitors and may prevent acquired resistance to treatment in tumors. MR: The health and welfare of the force is partially determined by the health and welfare of their supportive families. Military missions benefit when the Warfighters' families are healthy and well.	*Presentation: 1* *Funding: 1 (NIH K08)*

Log Number/ Amount/ Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Pediatric Cancer				
CA110045 $80,401.50 Closed	Garcia/ University of North Carolina at Chapel Hill	Aspm, a Key Element in Medulloblastoma Pathogenesis and a Novel Target for Treatment	RP: To test the hypothesis that Aspm, a growth-promoting gene required for cerebellar development, is subsequently drafted into the process of medulloblastoma formation. Found that Aspm becomes co-opted during medulloblastoma formation to support tumor growth by reducing stress to genomic DNA during cell division. Also, found that targeting Aspm can reduce medulloblastoma growth. MR: The health and welfare of the force is partially determined by the health and welfare of their supportive families. Military missions benefit when the Warfighters' families are healthy and well.	*Award terminated early because the PI received a second postdoctoral position at the BioDonostia Institute in San Sebastian*
CA110089 $381,600 Pending Closeout	Shi/ University of Texas Southwestern Medical Center at Dallas	Function of Brg1 Chromatin Remodeling Factor in Sonic Hedgehog-Dependent Medulloblastoma Initiation and Maintenance	RP: To determine the function of Brg1 in Shh signaling-activated medulloblastoma tumor formation and progression. Results show that the chromatin remodeler Brg1 is required for medulloblastoma growth in primary culture and that its deletion inhibits progression. This indicates that the chromatin remodeling complex BAF, through Brg1, is a therapeutic target for Shh-type medulloblastoma. MR: The health and welfare of the force is partially determined by the health and welfare of their supportive families. Military missions benefit when the Warfighters' families are healthy and well.	*Publications: 4* *Presentations: 2*

Log Number/ Amount/ Status	PI/ Organization	Application Title	Research Project (RP) and Military Relevance (MR)	Outcomes
Pediatric Cancer				
CA110407 $308,584 Closed	Jedlicka/ University of Colorado, Denver, Anschutz Medical Campus	Hypoxia in Ewing Sarcoma Stem Cell Properties and Drug Resistance	RP: To evaluate the inhibition of hypoxia inducible factor complex using microRNAs to see if they will inhibit the stem cell-like properties of Ewing Sarcoma cells, thus increasing their sensitivity to chemotherapy. Determined that the hypoxia response is mixed with both tumor promotional and tumor inhibitory effects in Ewing Sarcoma. A new, more specific, target downstream of HIF1α, KDM3A, has been identified and was established to be an important tumor and metastasis promoter in Ewing Sarcoma as well as a novel therapeutic target. MR: The health and welfare of the force is partially determined by the health and welfare of their supportive families. Military missions benefit when the Warfighters' families are healthy and well.	*Publication: 1* *Presentation: 1* *Funding obtained: 2*