



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

PERSONNEL AND
READINESS

FEB 17 2022

The Honorable Jon Tester
Chairman
Subcommittee on Defense
Committee on Appropriations
United States Senate
Washington, DC 20510

Dear Mr. Chairman:

The Department's response to Senate Report 116-103, page 238, accompanying S. 2474, the Department of Defense Appropriations Bill, 2020, and House Report 116-84, page 308, accompanying H.R. 2968, the Department of Defense Appropriations Bill, 2020, which request a report on the Peer-Reviewed Cancer Research Program (PRCRP), is enclosed.

The report summarizes the Fiscal Year (FY) 2020 PRCRP research award topics and investments per topic area; discusses relevance of the PRCRP research to Service members and their families; and covers FY 2009-FY 2019 PRCRP research award outcomes. The FY 2020 PRCRP funded 86 of the 600 full applications received (a 16 percent funding rate), which represents 98 separate awards. The Department expects outcomes by the end of the award performance periods, which span 2 to 4 years.

Thank you for your continued strong support for the health and well-being of our Service members, veterans, and families. I am sending similar letters to the other congressional defense committees.

Sincerely,

A handwritten signature in black ink, appearing to read "Gilbert R. Cisneros, Jr.", written in a cursive style.

Gilbert R. Cisneros, Jr.

Enclosure:
As stated

cc:
The Honorable Richard C. Shelby
Vice Chairman



PERSONNEL AND
READINESS

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

FEB 17 2022

The Honorable Betty McCollum
Chair
Subcommittee on Defense
Committee on Appropriations
U.S. House of Representatives
Washington, DC 20515

Dear Madam Chair:

The Department's response to Senate Report 116-103, page 238, accompanying S. 2474, the Department of Defense Appropriations Bill, 2020, and House Report 116-84, page 308, accompanying H.R. 2968, the Department of Defense Appropriations Bill, 2020, which request a report on the Peer-Reviewed Cancer Research Program (PRCRP), is enclosed.

The report summarizes the Fiscal Year (FY) 2020 PRCRP research award topics and investments per topic area; discusses relevance of the PRCRP research to Service members and their families; and covers FY 2009-FY 2019 PRCRP research award outcomes. The FY 2020 PRCRP funded 86 of the 600 full applications received (a 16 percent funding rate), which represents 98 separate awards. The Department expects outcomes by the end of the award performance periods, which span 2 to 4 years.

Thank you for your continued strong support for the health and well-being of our Service members, veterans, and families. I am sending similar letters to the other congressional defense committees.

Sincerely,

A handwritten signature in black ink, appearing to read "Gilbert R. Cisneros, Jr.", written in a cursive style.

Gilbert R. Cisneros, Jr.

Enclosure:
As stated

cc:
The Honorable Ken Calvert
Ranking Member



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

PERSONNEL AND
READINESS

FEB 17 2022

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

Dear Mr. Chairman:

The Department's response to Senate Report 116-103, page 238, accompanying S. 2474, the Department of Defense Appropriations Bill, 2020, and House Report 116-84, page 308, accompanying H.R. 2968, the Department of Defense Appropriations Bill, 2020, which request a report on the Peer-Reviewed Cancer Research Program (PRCRP), is enclosed.

The report summarizes the Fiscal Year (FY) 2020 PRCRP research award topics and investments per topic area; discusses relevance of the PRCRP research to Service members and their families; and covers FY 2009-FY 2019 PRCRP research award outcomes. The FY 2020 PRCRP funded 86 of the 600 full applications received (a 16 percent funding rate), which represents 98 separate awards. The Department expects outcomes by the end of the award performance periods, which span 2 to 4 years.

Thank you for your continued strong support for the health and well-being of our Service members, veterans, and families. I am sending similar letters to the other congressional defense committees.

Sincerely,

A handwritten signature in black ink, appearing to read "Gilbert R. Cisneros, Jr.", written in a cursive style.

Gilbert R. Cisneros, Jr.

Enclosure:
As stated

cc:
The Honorable James M. Inhofe
Ranking Member



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

PERSONNEL AND
READINESS

FEB 17 2022

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

Dear Mr. Chairman:

The Department's response to Senate Report 116-103, page 238, accompanying S. 2474, the Department of Defense Appropriations Bill, 2020, and House Report 116-84, page 308, accompanying H.R. 2968, the Department of Defense Appropriations Bill, 2020, which request a report on the Peer-Reviewed Cancer Research Program (PRCRP), is enclosed.

The report summarizes the Fiscal Year (FY) 2020 PRCRP research award topics and investments per topic area; discusses relevance of the PRCRP research to Service members and their families; and covers FY 2009-FY 2019 PRCRP research award outcomes. The FY 2020 PRCRP funded 86 of the 600 full applications received (a 16 percent funding rate), which represents 98 separate awards. The Department expects outcomes by the end of the award performance periods, which span 2 to 4 years.

Thank you for your continued strong support for the health and well-being of our Service members, veterans, and families. I am sending similar letters to the other congressional defense committees.

Sincerely,

A handwritten signature in black ink, appearing to read "Gilbert R. Cisneros, Jr.", written in a cursive style.

Gilbert R. Cisneros, Jr.

Enclosure:
As stated

cc:
The Honorable Mike D. Rogers
Ranking Member

Report to the Congressional Defense Committees



**In Response to: Senate Report 116–103, Page 238,
Accompanying S. 2474, the Department of Defense
Appropriations Bill, 2020, and House Report 116–84, Page
308, Accompanying H.R. 2968, the Department of Defense
Appropriations Bill, 2020, on the Peer-Reviewed Cancer
Research Program**

February 2022

The estimated cost of this report for the Department of Defense (DoD) is approximately \$3,500.00 for Fiscal Years 2020–2021. This includes \$1,700.00 in expenses and \$1,800.00 in DoD labor.

Generated on October 26, 2021

RefID: 5-91F32A1

BACKGROUND AND PURPOSE

This report is in response to the request in Senate Report 116–103, page 238, accompanying S. 2474, the Department of Defense (DoD) Appropriations Bill, 2020, and House Report 116–84, page 308, accompanying H.R. 2968, the DoD Appropriations Bill, 2020, for the Assistant Secretary of Defense for Health Affairs to provide a report to the congressional defense committees on the status of the Peer-Reviewed Cancer Research Program (PRCRP). For each research area, the report includes the funding amount awarded; progress of the research; and relevance of the research to Service members and their families. This Fiscal Year (FY) 2020 update provides information on actively negotiated awards by the Congressionally Directed Medical Research Programs (CDMRP). Previous updates for FY 2009-FY 2019 are accessible at: <https://cdmrp.army.mil/prcrp/reports/reports>.

The Defense Health Agency manages the Defense Health Program (DHP) Research, Development, Test, and Evaluation (RDT&E) appropriations. The U.S. Army Medical Research and Development Command (USAMRDC) provides execution management for the DHP RDT&E PRCRP Congressional Special Interest funds. Any references to non-Federal entities are not intended as an endorsement of those entities.

FY 2020 PRCRP INTRODUCTION AND STATUS

Since the PRCRP’s inception in FY 2009, Congress has directed its appropriation amount and the different topic areas to receive funding (Table 1). Each FY, many factors affect the PRCRP investment portfolio, such as whether it includes a specific topic area; the number of applications received for each topic area; the scientific merit of each proposed research project and potential impact of its outcomes; and the appropriation amount with respect to the number of topic areas. The programmatic review considers each topic area to ensure a balanced portfolio with respect to the specific FY topic areas.

Table 1. PRCRP Appropriation and Topic Areas per Fiscal Year

Fiscal Year	Appropriation (Awards) [‡]	Topic Areas*
2009	\$16M (38)	\$4M, Melanoma and other skin cancers 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 various environments unique to a military lifestyle; and \$2M, Noninvasive cancer ablation treatment including selective targeting with nanoparticles
2010	\$15M (30)	Melanoma and other skin cancers; Pediatric brain tumors within the field of childhood cancer research; Genetic cancer research and genomic medicine; Kidney cancer; Blood cancer; Colorectal cancer; <i>Listeria</i> vaccine for cancer; and Radiation protection utilizing nanotechnology
2011	\$16M (44)	Melanoma and other skin cancers; Pediatric cancer research; Genetic cancer research; Kidney cancer; Blood cancer; Colorectal cancer; Pancreatic cancer; Mesothelioma; <i>Listeria</i> vaccine for cancer; and Radiation protection utilizing nanotechnology
2012	\$12.8M (27)	Melanoma and other skin cancers; Pediatric brain tumors; Genetic cancer; Pancreatic cancer; Kidney cancer; Blood cancer; Colorectal cancer; Mesothelioma; and <i>Listeria</i> vaccine for cancer

Fiscal Year	Appropriation (Awards)‡	Topic Areas*
2013	\$15M (27)	Melanoma and other skin cancers; Pediatric brain tumors; Genetic cancer; Pancreatic cancer; Kidney cancer; Blood cancer; Colorectal cancer; Mesothelioma; and Neuroblastoma
2014	\$25M (47)	Blood cancer; Colorectal cancer; Genetic cancer research; Kidney cancer; <i>Listeria</i> vaccine for cancer; Melanoma and other skin cancers; Mesothelioma; Myeloproliferative disorders; Neuroblastoma; Pancreatic cancer; Pediatric brain tumors; and Cancers related to radiation exposure
2015	\$50M (110)	Colorectal cancer; Genetic cancer research; Kidney cancer; <i>Listeria</i> vaccine for cancer; Liver cancer; Melanoma and other skin cancers; Mesothelioma; Myeloproliferative disorders; Neuroblastoma; Pancreatic cancer; and Stomach cancer
2016	\$50M (89)	Bladder cancer; Colorectal cancer; Immunotherapy; Kidney cancer; <i>Listeria</i> vaccine for cancer; Liver cancer; Lymphoma; Melanoma and other skin cancers; Mesothelioma; Myeloproliferative disorders; Neuroblastoma; Pancreatic cancer; Pediatric brain tumors; and Stomach cancer
2017	\$60M (92)	Bladder cancer; Brain cancer; Cancer in children, adolescents, and young adults; Colorectal cancer; Immunotherapy; <i>Listeria</i> -based regimens for cancer; Liver cancer; Lymphoma; Melanoma and other skin cancers; Mesothelioma; Neuroblastoma; Pancreatic cancer; Pediatric brain tumors; and Stomach cancer
2018	\$80M (114)	Adrenal cancer; Bladder cancer; Blood cancers; Brain cancer; Cancer in children, adolescents, and young adults; Colorectal cancer; Immunotherapy; <i>Listeria</i> -based regimens for cancer; Liver cancer; Lymphoma; Melanoma and other skin cancers; Mesothelioma; Myeloma; Neuroblastoma; Pancreatic cancer; Pediatric brain tumors; and Stomach cancer
2019	\$90M (103)	Bladder cancer; Blood cancers; Brain cancer; Cancer in children, adolescents, and young adults; Colorectal cancer; Immunotherapy; <i>Listeria</i> -based vaccines for cancer; Liver cancer; Lymphoma; Mesothelioma; Neuroblastoma; Pancreatic cancer; Pediatric brain tumors; Rare cancers; and Stomach cancer
2020	\$110M (98)	Bladder cancer; Blood cancers; Brain cancer; Colorectal cancer; Esophageal cancer; Head and neck cancer; Immunotherapy; Liver cancer; Mesothelioma; Metastatic cancers; Neuroblastoma; Pediatric, adolescent, and young adult cancers; Pediatric brain tumors; and Stomach cancer

*Congressional language designates topic areas (as published in the Public Law, Congressional Record, and post-Presidential signature communications for clarification on language).

‡Number of awards represents all open, pending closeout, and closed awards, and does not include withdrawals.

STATUS

During October-November 2020, external panels of experts (including scientists, clinicians, consumers, active duty Service members, and veterans) conducted a scientific peer review of the applications received for FY 2020 PRCRP funding. The panels evaluated each application on its technical merit and anticipated impact on patient outcomes. The second tier of review, programmatic review (held in December 2020-February 2021), included discussions by experts in the field, including the FY 2020 Programmatic Panel members for the PRCRP and ad hoc reviewers (<https://cdmrp.army.mil/prcrp/panels/panels>). These experts (scientists, clinicians, consumers, active duty Service members, and veterans) assessed the applications based on their respective scientific peer-reviewed ratings and relevance to military health, and compared each peer-reviewed application with the portfolio composition and intent of the published program announcement to ensure a balanced portfolio and alignment with programmatic intent.

Following, the experts recommended applications for funding that were scientifically sound and best met the program's interests and goals.

In FY 2020, the PRCRP funded 86 applications (representing 98 separate awards) of the 600 full applications received, for a 16 percent funding rate totaling \$97,148,876. The remaining \$12,851,124 of the FY 2020 PRCRP appropriation is directed toward administrative and management costs in support of these PRCRP projects and DoD withholds to include USAMRDC withholds, Small Business Innovation Research/Small Business Technology Transfer Programs allocations, and CDMRP management costs (totaling 6.5 percent).

The PRCRP awarded all FY 2020 research funds by September 30, 2021. The Department expects outcomes by the end of each period of performance, which spans 2 to 4 years from the start date of an award. Table 2 shows the FY 2020 total recommended research funding by topic area. Table 3 summarizes the types of FY 2020 PRCRP funding opportunities.

Table 2. FY 2020 Total Research Dollars Invested per Topic Area

Topic Area	Number of Awards	Total Recommend for Funding
Bladder Cancer	10	\$8,423,391
Blood Cancers	10	\$9,982,909
Brain Cancer	9	\$9,182,464
Colorectal Cancer	11	\$10,633,234
Esophageal Cancer	4	\$4,311,951
Head and Neck Cancers	8	\$8,858,543
Immunotherapy	7	\$6,359,546
Liver Cancer	8	\$6,753,957
Mesothelioma	2	\$2,148,614
Metastatic Cancers	3	\$3,496,809
Neuroblastoma	3	\$4,773,088
Pediatric Brain Tumor	7	\$6,120,864
Pediatric, Adolescent, and Young Adult Cancers	11	\$12,286,688
Stomach Cancer	5	\$3,816,818

Table 3. FY 2020 PRCRP Funding Opportunities

FY 2020 Funding Opportunity	Intent	Funding Per Award
Idea Award	Studies focused on innovation	\$500,000
Career Development Award	Investment in Early Career Investigators	Fellow Option \$400,000 Scholar Option \$800,000
Virtual Cancer Center Award	Director/Deputy Director oversight of a virtual researcher network of researchers (Scholars) tying together all cancers	\$1,250,000
Impact Award	Studies focused on near-term clinical impact	\$1,000,000
Translational Team Science Award	Correlative studies focused on informing clinical practice	\$1,500,000
Behavioral Health Science Award	Studies intended to improve survivorship and patient outcomes	\$1,000,000

MILITARY HEALTH AND CANCER: SERVICE MEMBERS AND THEIR FAMILIES

Congressional language requested that PRCRP-funded research be relevant to Service members and their families. The PRCRP develops its investment strategy around relevance to military health concerns. The FY 2020 PRCRP addressed these core capabilities by *requiring* that all applications address at least one of the FY 2020 PRCRP relevant military health focus areas, presented in Table 4.

Table 4. FY 2020 Relevance to Military Focus Areas

Environmental Exposures	Environmental/exposure risk factors associated with cancer
Mission Readiness	Gaps in cancer prevention, early detection/diagnosis, prognosis, and/or treatment that may affect the general population, but have a particularly profound impact on the health and well-being of military Service members, veterans, and their beneficiaries Gaps in quality of life and/or survivorship that may affect the general population, but have a particularly profound impact on the health and well-being of military Service members, veterans, and their beneficiaries

ENVIRONMENTAL EXPOSURES

Service members deployed worldwide encounter multiple dangerous exposures that play a role in cancer development. Exposures linked to increased cancer risk include, but are not limited to,

chemical weapons or storage, ionizing radiation, herbicides, electromagnetic fields, jet fuel, organic materials, biological agents, and ultraviolet radiation, among others (Table 5). The Department of Veterans Affairs (VA) has acknowledged certain exposures increase cancer risk among Service members and their families (<https://www.publichealth.va.gov/exposures/index.asp>).

Table 5. FY 2020 PRCRP Topic Areas: Cancer Risk and Military Service

Topic Areas	Relevance to Military Health
Bladder Cancer (refs. 5-7)	Bladder cancer (BCa) is the fourth most common cancer among U.S. Service members. Along with smoking, occupational exposure to chemical carcinogens present in paints and dyes increases BCa risk.
Blood Cancers (Leukemia, Lymphoma, Myeloma) (refs. 4, 9)	Exposure to toxic chemicals/herbicides shown to increase risk; the VA acknowledged the association of Agent Orange and other herbicides with blood cancers among veterans. Ionizing radiation exposure has demonstrated correlation with increased risk of blood cancer.
Adult and Pediatric Brain Cancer (Brain Cancer, Neuroblastoma, and Pediatric Brain Tumors) (refs. 10, 11)	<u>Adult Brain Cancer:</u> Occupational exposure link. Patients with traumatic brain injury are at increased risk of acquiring brain tumors (hazard ratio of 4.67). <u>Pediatric Brain Tumor (PBT)/Neuroblastoma:</u> In all childhood populations, PBT has the highest mortality rates of any childhood cancer; affects mission readiness of Service members with children.
Cancers in Children (0–14 years of age), Adolescents (15–24 years of age), and Young Adults (25–39 years of age) (refs. 11, 12)	Cancers incurred by active duty Service members' support systems (e.g., family members) affect mission readiness: 86 percent of the military are under 39 years of age (adolescents and young adults 15–39 years of age).
Gut Cancers (Esophageal Cancer, Colorectal, Liver, Stomach Cancer) (refs. 13-15)	<u>Esophageal Cancer:</u> VA acknowledged connection to military Service. <u>Colorectal Cancer:</u> Screening of active duty Service members decreases mortality rates. A 2014 report showed that 72 percent of veterans are up-to-date on age-related screening; other studies demonstrate a potential implication of infectious diseases with increased mortality rates. <u>Liver Cancer:</u> The veteran population has an increased hazard ratio: increased alcohol use leads to increased risk.

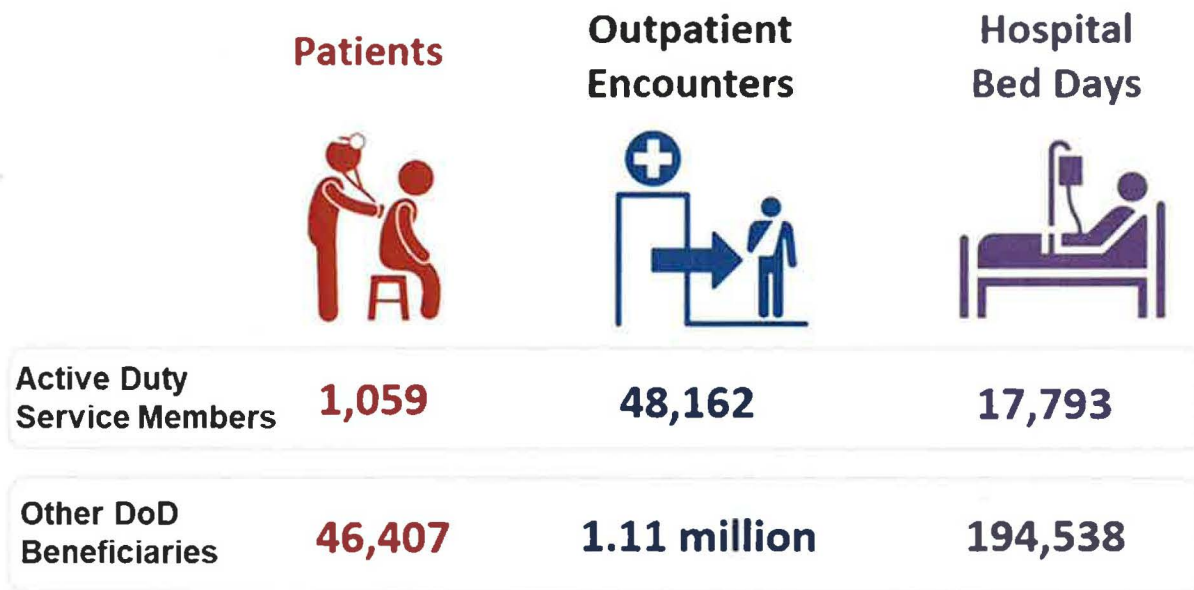
Topic Areas	Relevance to Military Health
	<u>Stomach Cancer</u> : Due to increased exposure (deployment in globally endemic areas) to infectious agents (<i>Helicobacter pylori</i>), veterans may be at increased risk.
Head and Neck Cancers (ref. 16)	Agent Orange, smoking, alcohol consumption, and human papillomavirus (HPV) infection have demonstrated associations with oropharyngeal, nasopharyngeal, and laryngeal cancers. Over 70 percent of head and neck cancers are associated with HPV infection, the majority of which are among men.
Mesothelioma (ref. 17)	Veterans account for more than 33 percent of all cases in the United States; asbestos exposure is the leading cause.
Metastatic Cancers (ref. 18)	Cancer metastasis is the major cause of cancer morbidity and mortality, accounting for an estimated 90 percent of cancer deaths.

MISSION READINESS

A Service member's cancer diagnosis affects not only the individual Soldier, Sailor, Marine, or Airman, but also the Service member's entire unit and mission. Each Service member plays a crucial role in mission readiness that may be affected by a cancer diagnosis of the Service member or family member (Table 5). Research that improves survival, while minimizing side effects, will have a major impact on mission readiness by enabling an active duty Service member to return to full duty. Additionally, mission readiness includes ensuring that family members receive world-class healthcare. Service members become affected when a member of their family or support system receives a cancer diagnosis. Time off to assist in the care, recovery, and well-being of family members will affect the overall unit force readiness.

Cancer not only directly affects the military's capabilities, but also indirectly places a burden on the Military Health System (MHS). Data provided by the Armed Forces Health Surveillance Branch, based on electronic records within Defense Medical Surveillance System (DMSS), demonstrated the impact of cancer care on the MHS. Figure 1 shows the MHS medical encounters for leukemia (2010–2019), a cancer type within the PRCRP's Blood Cancers topic area.

Figure 1. Military Health System Medical Encounters for Leukemia (2010-2019)*



*Data provided by the Armed Forces Health Surveillance Branch, based on electronic records within DMSS. Does not include care received outside the MHS. Includes all MHS inpatient and outpatient encounters where the first (primary) diagnosis was for leukemia. Active Component Service members (ACSM) does not include Activated Reserve and Activated National Guard. This does not include care received while deployed or any care received outside MHS that was not processed through TRICARE (i.e., care covered by other insurance sources or care paid for entirely out of pocket). Other DoD beneficiaries include: National Guard/Reserve members; family members of ACSM and National Guard/Reserve members; former Service members; and family members of former Service members.

A report commissioned by The Leukemia & Lymphoma Society found that the treatment cost for blood cancers during the first year following diagnosis is \$156,000 per patient (The Leukemia & Lymphoma Society, 2018). The costs for three years of follow-on care vary, dependent on blood cancer type (e.g., \$200,000 for chronic leukemia to over \$800,000 for acute leukemia). Other cancers, such as bladder cancer, have mean lifetime costs that can exceed \$200,000 (Aly et al, 2020). Studies show the costs of national cancer care in 2020 were \$208 billion (National Cancer Institute, Financial Burden of Cancer Care). The MHS and VA burden include costs for active duty Service members, their families, veterans, and other military beneficiaries.

MAJOR PRCRP ACCOMPLISHMENTS

Select outcomes and accomplishments funded by the PRCRP that may have a major health impact on active duty Service members and their families, veterans, and the public, are described below.

XPOVIO® (selinexor) for Blood Cancers

Addressing the key elements of cancer research and patient care is crucial to PRCRP’s mission. In FY 2013, the PRCRP funded research conducted by The Ohio State University, which aimed at identifying novel therapeutic targets for blood cancer treatment, using chronic lymphocytic

leukemia as the model system (https://cdmrp.army.mil/prcrp/research_highlights/21lapalombella_highlight). This research resulted in the discovery that overexpression of the protein exportin (XPO1) led to functional disruption of tumor suppressor genes. This work advanced development of the drug selinexor in the initial phase 1 study and led to combination studies of XPOVIO® (selinexor) with the drug ibrutinib. In 2020, the Food and Drug Administration (FDA) approved XPOVIO® for the treatment of relapsing multiple myeloma and diffuse large B-cell lymphoma; both blood cancers are known to be associated with military service, as noted by the VA (U.S. Department of Veteran Affairs, Agent Orange Exposure and VA Disability Compensation). New analogs of this drug are under development to expand treatment for a variety of different cancers.

Topical Nitric Oxide Therapy to Treat and Prevent HPV Associated Cancers

Novan Inc. developed an antiviral medication that may be self-administered as a potential treatment for HPV-related cancers (i.e., cervical, vaginal, vulvar, penile, and anal cancers). Funded by the PRCRP in FY 2018, this work resulted in the design of vehicle prototypes capable of self-delivery via a suppository with purity, melting point profile, macroscopic appearance, and study of microscopic appearance. This effort also established a dosing and application frequency that successfully inhibits HPV-18 replication while minimizing cytotoxicity. Final performance testing is underway. Cervical, vaginal, vulvar, penile, and anal cancers have demonstrated associations with high-risk HPV infection (i.e., HPV-16 and HPV-18). Anti-HPV vaccine compliance approximates 40 percent in the United States; adults over 40 years of age are not eligible for vaccination, leaving a large population at risk for these cancers. Early treatment of intraepithelial neoplasia may halt development of cancers and save lives. As such, an easy-to-use topical treatment would advance the field of early HPV treatment and prevention of HPV-related cancer development considerably, while protecting Service members and their families.

Synergistic Immuno-Photo-Nanotherapy (SYMPHONY) for Bladder Cancer

The FY 2016 PRCRP awarded research conducted at Duke University that demonstrated eradication of focal and distant bladder cancer through a combination of immunotherapy and photothermal nanotherapy through a two-pronged approach. With a combination of immune checkpoint inhibitors and plasmonic gold nanostar-mediated photothermal therapy, primary bladder tumors received treatment, while the activated immune system attacked distant metastasis in mice. This proof-of-principle experiment led to the development of SYMPHONY, a potential new therapeutic technology for bladder cancer. Therapeutic technologies that enhance the immune system to fight cancer represent a new horizon of treatments with the potential to impact multiple and different cancers relevant to military health.

Denosumab: Central Tolerance Blockade to Augment Immunotherapy in Melanoma

The FY 2014 PRCRP awarded the University of North Carolina, Chapel Hill, to investigate whether blocking central tolerance enhances the immune checkpoint blockade to treat melanoma. A key mediator of central tolerance is the autoimmune regulator, Aire. This study revealed that a subset of cells (mTECs) express receptor activator of nuclear factor kappa-B ligand (RANKL), which activates Aire and leads to deletion of T cells. Antibodies against RANKL block Aire

expression and decrease mTECs, therefore increasing activation of T cells and harnessing the power of the immune system against melanoma. Denosumab is an FDA-approved antibody therapeutic that targets RANKL. This study demonstrated a synergistic effect of denosumab with checkpoint inhibitors anti-CTLA4 and anti-PD1, significantly decreasing tumor growth and prolonged survival. The results of this PRCRP-funded project led to the development of a phase 2 clinical trial for stage III/IV melanoma patients (cutaneous and mucosal). Patient recruitment for this trial is underway at the University of North Carolina Lineberger Comprehensive Cancer Center.

Other accomplishments may be reviewed at the PRCRP webpage for research highlights (<https://cdmrp.army.mil/prcrp/highlights>). A summary of research outcomes funded by the PRCRP from FY 2009 through FY 2019 is shown in Table 6.

Table 6. Summary of FY 2009-FY 2019 PRCRP Research Outcomes

Reported Research Outcome Type	Number of Outcomes
Follow-On Funding Obtained	199
Patents (including provisional)	89
Presentations	1373
Publications	1184
Total Reported Outcomes	2845

FY 2020 PRCRP TOPIC AREAS: RELEVANCE TO MILITARY HEALTH

Cancer research has a profound impact on reducing the burden of cancer on military families and improving force readiness. Potential cancer risks and impacts on military health are shown in Table 5. Successful new studies may lead to new ways to prevent cancer development, better diagnostic/detection methods, new prognostic information, potentially novel treatments, and better ways to cope with quality of life issues.

New FY 2020 PRCRP Initiative in Response to Military Health and Cancer: FY 2020 Virtual Cancer Center

To address the needs of active duty Service members, their families, and other military beneficiaries, the PRCRP developed a new investment strategy to address cancer, employing the idea of convergence science. Convergence science, as defined by the National Science Foundation (<https://www.nsf.gov/od/oia/convergence/index.jsp>), is “a means of solving vexing research problems, in particular, complex problems focusing on societal needs.”

For FY 2020, PRCRP offered and invested in the Virtual Cancer Center Director Award (VCCDA) and the Career Development Award-Scholar Option to establish the Convergent Science Virtual Cancer Center (CSVCC). The focus of the groundbreaking CSVCC is to catalyze training of early-career independent investigators (Scholars) in convergent science, thus exploiting the idea of intersecting multiple disciplines and cancers together in a cross-pollinating research network. Within the scope of the CSVCC, the PRCRP integrates research from

different disciplines and cancers to forge a new frontier toward the commonalities of cancer that will lead to answers for military health in cancer research and care. Representatives from the Cedars Sinai Cancer Center and University of Southern California serve in CSVCC leadership roles to lead the next generation of Career Development Award Scholars in a collegial, highly dynamic, and cutting-edge cancer center. Total FY 2020 PRCRP investment of in this initiative (VCCDA and Career Development Award Scholars) is \$12.6M.

The CSVCC includes a Convergence Council (CC) with a Special Advisor on Military Health to integrate military health concerns within the heart of the research. The CC membership of 19 scientists, clinicians, entrepreneurs, administrators, and former military officers serves as an external advisory board for the CSVCC. Five of its 19 members offer experience with military and veterans' health. By emphasizing military health and relevance, the CSVCC maximizes the benefit of the research to Service members and their families, while training the next generation of future leaders in cancer research focused on military needs.

SUMMARY

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

REFERENCES

1. The Leukemia & Lymphoma Society. 2018. The cost burden of blood cancer care: A longitudinal analysis of commercially insured patients diagnosed with blood cancer. Milliman Research Report. <https://www.lls.org/sites/default/files/Milliman%20study%20cost%20burden%20of%20blood%20cancer%20care.pdf>.
2. Aly A, Johnson C, Doleh Y, et al. The Real-World Lifetime Economic Burden of Urothelial Carcinoma by Stage at Diagnosis. *J Clin Pathw*. 2020;6(4):51-60.
3. National Cancer Institute. Financial Burden of Cancer Care. https://progressreport.cancer.gov/after/economic_burden.
4. U.S. Department of Veteran Affairs. Agent Orange Exposure and VA Disability Compensation. <https://www.va.gov/disability/eligibility/hazardous-materials-exposure/agent-orange/related-diseases/>.
5. Avritscher EB, Cooksley CD, Grossman HB, et al. Clinical model of lifetime cost of treating bladder cancer and associated complications. *Urology*. 2006;68(3):549-553. doi:10.1016/j.urology.2006.03.062
6. Schroeck FR, Sirovich B, Seigne JD, Robertson DJ, Goodney PP. Assembling and validating data from multiple sources to study care for Veterans with bladder cancer. *BMC Urol*. 2017;17(1):78. Published 2017 Sep 6. doi: 10.1186/s12894-017-0271-x
7. Uhlig A, Strauss A, Seif Amir Hosseini A, et al. Gender-specific Differences in Recurrence of Non-muscle-invasive Bladder Cancer: A Systematic Review and Meta-analysis. *Eur Urol Focus*. 2018;4(6):924-936. doi: 10.1016/j.euf.2017.08.007
8. Zullig LL, Sims KJ, McNeil R, et al. Cancer Incidence Among Patients of the U.S. Veterans Affairs Health Care System: 2010 Update. *Mil Med*. 2017;182(7):e1883-e1891. doi: 10.7205/MILMED-D-16-00371
9. U.S. Department of Veterans Affairs. Public Health: Military Exposures. <https://www.publichealth.va.gov/exposures/index.asp>.
10. Chen YH, Keller JJ, Kang JH, Lin HC. Association between traumatic brain injury and the subsequent risk of brain cancer. *J Neurotrauma*. 2012;29(7):1328-1333. doi: 10.1089/neu.2011.2235
11. Centers for Disease Control and Prevention: Declines in Cancer Death Rates Among Children and Adolescents in the United States, 1999-2014. https://www.cdc.gov/cancer/hpv/basic_info/cancers.htm.

12. Department of Defense, Office of the Deputy Assistant Secretary of Defense for Military Community and Family Policy. 2018 Demographics Report. <https://download.militaryonesource.mil/12038/MOS/Reports/2018-demographics-report.pdf>.
13. Brennan CA, Garrett WS. Gut Microbiota, Inflammation, and Colorectal Cancer. *Annu Rev Microbiol.* 2016;70:395-411. doi: 10.1146/annurev-micro-102215-095513
14. The association of selected cancers with service in the U.S. military in Vietnam. III. Hodgkin's disease, nasal cancer, nasopharyngeal cancer, and primary liver cancer. The Selected Cancers Cooperative Study Group. *Arch Intern Med.* 1990;150(12):2495-2505. doi: 10.1001/archinte.150.12.2495
15. National Cancer Institute: Helicobacter pylori and Cancer. <https://www.cancer.gov/about-cancer/causes-prevention/risk/infectious-agents/h-pylori-fact-sheet>.
16. Centers for Disease Control and Prevention. Cancers Associated with Human Papillomavirus (HPV). https://www.cdc.gov/cancer/hpv/basic_info/cancers.htm.
17. Till JE, Beck HL, Boice JD, et al. Asbestos Exposure and Mesothelioma Mortality among Atomic Veterans [published online ahead of print, 2018 Dec 4]. *Int J Radiat Biol.* 2018;1-15. doi: 10.1080/09553002.2018.1551641
18. Guan X. Cancer metastases: challenges and opportunities. *Acta Pharm Sin B.* 2015;5(5):4021418. doi: 10.1016/j.apsb.2015.07.005