The Congressionally Directed Medical Research Programs (CDMRP) was established in 1992, when Congress first appropriated funds for the Breast Cancer Research Program. Since then, CDMRP has been responsible for managing more than $14 billion in Congressional appropriations. CDMRP is comprised of over 30 programs which fund groundbreaking, high impact, meritorious research that benefits military personnel and their families, Veterans, and the American public. Funds for CDMRP are added annually to the Department of Defense budget by Congress to support individual programs such as the Peer Reviewed Cancer Research Program (PRCRP).

The PRCRP was established in fiscal year 2009 (FY09) to support innovative research in cancers and other specialty areas specifically designated by Congress as relevant to Service members and their families. From FY09 through FY19, Congress has appropriated $429.8M to PRCRP, which in turn has invested in cancer research covering 25 topic areas.* PRCRP-funded research has advanced knowledge on the prevention, early detection, diagnosis, and treatment of cancer that benefits Service members, their families, and the American public.

**Vision:** To advance mission readiness of U.S. military members affected by cancer and to improve quality of life by decreasing the burden of cancer on Service members, their families and the American public

**Mission:** To successfully promote high-impact research for cancer prevention, detection, treatment, and survivorship

**Congressional Appropriations**

FY09-FY19:

$429.8 million (M)

616 Awards Funded

25 Topic Areas

*As of publication the FY19 applications were under review.
### PRCRP Topic Areas

The PRCRP funds a variety of cancer topic areas based on Congressional language. In the inaugural year of PRCRP, 4 topic areas were offered. Since then, 25 different topic areas have been funded by the PRCRP. It is important to note that the topic areas are designated by Congress, so topic areas may change from year to year.

### PRCRP Milestones

**FY09 - $16M - 4 Topic Areas**

Congress establishes PRCRP with four Topic Areas and an appropriation of $16M.

**FY14 - $25M - 12 Topic Areas**

In response to the Fukushima Nuclear Power Plant disaster in Japan, Cancers Related to Radiation Exposure is included as a Topic Area this year. PRCRP funded 2 awards for a total of $0.92M.

**FY15 - $50M - 11 Topic Areas**

Congress appropriates $50M to PRCRP. PRCRP establishes the Translational Team Science Award mechanism to support multi-investigator, multidisciplinary teams to perform translational, clinical studies.

**FY18 - $80M - 17 Topic Areas**

Congress appropriates $80M to PRCRP. PRCRP establishes the Impact Award, intended to support paradigm shifting cancer research with the goal of improving patient care and treatment outcomes. PRCRP funds four clinical trials in the areas of melanoma, liver cancer, and pancreatic cancer.

**FY19 - $90M - 15 Topic Areas**

Congressional appropriation for PRCRP is $90M. Rare Cancers is added as a topic area. Rare cancers are defined as cancers that occur in fewer than 15 out of 100,000 people each year.

### FY09-FY18 PRCRP Investment by Topic Area (% Dollars)

<table>
<thead>
<tr>
<th>Topic Area</th>
<th>FY09-FY18 Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Invasive Cancer Ablation (FY09)</td>
<td>1%</td>
</tr>
<tr>
<td>Pediatric Brain Tumors (FY09-FY18)</td>
<td>1%</td>
</tr>
<tr>
<td>Neuroblastoma (FY13-FY18)</td>
<td>2%</td>
</tr>
<tr>
<td>Myeloproliferative Disorders (FY14-FY18)</td>
<td>1%</td>
</tr>
<tr>
<td>Mesothelioma (FY11-FY18)</td>
<td>4%</td>
</tr>
<tr>
<td>Stomach Cancer (FY15-FY18)</td>
<td>5%</td>
</tr>
<tr>
<td>Adrenal Cancer (FY18)</td>
<td>1%</td>
</tr>
<tr>
<td>Bladder Cancer (FY15-FY18)</td>
<td>5%</td>
</tr>
<tr>
<td>Blood Cancer (FY10-FY18, FY18)</td>
<td>7%</td>
</tr>
<tr>
<td>Brain Cancer (FY17-FY18)</td>
<td>2%</td>
</tr>
<tr>
<td>Cancers Related to Radiation Exposure (FY14)</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Cancer in Children, Adolescents and Young Adults (FY08-FY18)</td>
<td>4%</td>
</tr>
</tbody>
</table>
Military Health

Congressional language has directed that research funded by the PRCRP should be relevant to Service members and their families. As a research funding program, the PRCRP crafts its investment strategy around the requirement to be relevant to military health concerns. Some cancers, such as mesothelioma, stomach, and blood cancers, are risk factors for active duty Service members due to exposures related to military service and deployment. Other cancers may affect the military in that a diagnosis will impact mission-readiness. All applications submitted to and funded by the PRCRP must show relevance to military health. In FY19, there are two military health focus areas.

PRCRP FY19 Military Health Focus Areas

- Environmental/exposure risk factors associated with cancer
- Gaps in cancer prevention, early detection/diagnosis, prognosis, treatment, and/or survivorship that may impact mission readiness and the health and well-being of military members, Veterans, their beneficiaries, and the general public

Occupational and environmental hazards may increase the risk of developing certain cancers as shown in the table below.

<table>
<thead>
<tr>
<th>Risk</th>
<th>Related Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agent Orange and Other Herbicides</td>
<td>Soft tissue sarcoma, hodgkin’s and non-hodgkin’s lymphoma, chronic lymphocytic leukemia (CLL), multiple myeloma</td>
</tr>
<tr>
<td>Asbestos</td>
<td>Mesothelioma, bladder cancer</td>
</tr>
<tr>
<td>Infectious Agents</td>
<td>Epstein-barr virus: lymphoma, oral cavity cancer</td>
</tr>
<tr>
<td></td>
<td>Hepatitis B and hepatitis C viruses: liver cancer</td>
</tr>
<tr>
<td></td>
<td>Human immunodeficiency virus: kaposi sarcoma, lymphoma, cervical, anal, throat, liver cancer</td>
</tr>
<tr>
<td></td>
<td>Human papilloma virus: cervical, oral, vulvar, vaginal, penile, anal cancer</td>
</tr>
<tr>
<td></td>
<td>Human T-cell lymphotropic virus type 1: adult T-cell lymphoma</td>
</tr>
<tr>
<td></td>
<td>Helicobacter pylori: gastric cancer</td>
</tr>
<tr>
<td>Alcohol</td>
<td>Oral, esophageal, liver, colorectal cancer</td>
</tr>
</tbody>
</table>

Strategic Plan

The PRCRP strategic plan outlines the current goals for the program, including research priorities and how research outcomes will be tracked. The current PRCRP strategic plan can be found on CDMRP’s website (https://cdmrp.army.mil/prcrp/default). Through funding opportunities, the PRCRP offers investigators a means toward pursuing avenues of research that are under developed in cancer. Multiple cancers under the umbrella of the PRCRP not only lack adequate funding to make strides in clinical care, but also lack the community of investigators to commit to a career in research and study of that topic area.

FY15-FY18 Investment by Award Mechanism Type (% Dollars)

FY15-FY18 PRCRP Investment by Military Health Focus Area (% Dollars)
Marisa Ajdelman – Voice for Stomach Cancer Research

Stomach cancer is the fourth leading cause of cancer-related deaths worldwide but is considered uncommon in the United States. Primary care physicians in the US are not familiar with the symptoms and therefore, patients may be misdiagnosed or diagnosed late in their disease. Ms. Marisa Ajdelman is one of those patients, having lived through a misdiagnosis, a re-staging, and a recurrence.

Marisa’s story is a struggle that is not uncommon for stomach cancer patients in the US. Her journey began with unexplained weight loss in 2016. Her ailments advanced to the point that she was unable to eat normally sized portions, and she consistently felt pain after meals. Marisa was tested for various possible gastrointestinal conditions, including Helicobacter pylori infection, for which she was treated. However, the harsh triple antibiotic protocol proved unsuccessful in clearing the infection. Marisa then underwent an ultrasound that detected ascites in the abdominal cavity—a highly concerning finding that led to an emergency endoscopy which in April 2017 resulted in her Stage 4 stomach cancer diagnosis. A second opinion and extensive re-testing at Stanford Health Care’s gastrointestinal oncology clinic resulted in a re-staging to Stage 3b. In addition to chemotherapy, Marisa also underwent multiple surgeries, both exploratory and curative, including an extensive total gastrectomy with pancreatico-splenectomy. By December 2017, she showed no evidence of the disease. However, in June 2018, when a tumor on her right ovary was detected, she learned that her stomach cancer had recurred. After an additional curative surgery, followed by 12 cycles of chemotherapy, Marisa was declared clear of cancer once again in early January 2019.

Throughout her journey, including multiple surgeries and 18 combined cycles of chemotherapy treatments, Marisa has been a passionate member of Hope for Stomach Cancer, a nonprofit organization with programs that help stomach cancer patients take steps to live the best life possible. A long-time successful global marketing manager, Marisa decided to go on long-term disability to devote her time and energy to her fight with stomach cancer. However, Marisa remains a positive community member. She volunteers with several causes that directly support stomach cancer research, and she is involved with various patient mentoring programs. Marisa values family time above all else, and her top priority is her 13-year-old son.

Marisa took her position as a member of FY18 PRCRP peer review panel very seriously, as her long and uncertain journey is so commonly shared among stomach cancer patients. She embraces her role as a survivor, empowered to discuss patient needs and priorities with researchers and medical practitioners. She hopes that more patients will actively educate themselves and others on the disease and engage in advocacy, as she does, for increased investment in research focused on earlier diagnosis and novel treatment therapies that will render more positive outcomes for advanced stomach cancer patients such as herself.
Nate Espeland – Fighting for the “Little Guy”

“As it relates to the PRCRP, no matter which sarcoma a person might have recently been diagnosed with, that person is now the ‘little guy,’ and I think it’s wonderful to be a part of an organization where research might already be out there, solely dedicated to treating that specific type of sarcoma, all thanks to the PRCRP.” – Nate Espeland

In 2005 Nate Espeland, an active duty Service member in the US Air Force, was diagnosed with liposarcoma, a rare type of cancer that affects soft tissues, such as muscles. With a tumor the size of a football in his left hamstring, Nate underwent chemotherapy, followed by tumor resection (surgery to remove the bulk of the mass). Upon investigating the tumor, his physicians were stunned to find that the cancer was growing just as rapidly as the chemotherapy was attacking it. Nate then underwent radiation therapy lasting until June 2006 to kill any remaining cancer cells. However, 5 months after he left the Air Force, in April 2007, the cancer returned. Over the next 5 years, Nate underwent further tumor resection and radiation therapy for six additional tumors in his pericardium, right calf, lung, right femur in two spots, and in his abdomen. Due to the aggressive nature of this type of sarcoma, Nate has had three hamstring muscles removed, three calf muscles removed, a knee replacement, and one femur replaced twice. Today, Nate has been cancer-free for 6 years.

Nate describes his journey as unpredictable. When he believed that he was completely healthy, the screening results would show that the cancer had aggressively spread. Other times, Nate was sure that the cancer had returned, but the scans would show no new evidence of disease. Given the lethality of this high-grade metastasized disease, Nate feels fortunate to have survived. He also believes that he would not be alive without a strong support system of family and friends. Nate works now as an Army air traffic controller; in his free time he enjoys being outdoors with his two dogs, and he is active with “Rein in Sarcoma,” a Midwest-based foundation that serves as a research, support, and education resource for families touched by sarcomas. He is a strong advocate of this organization because of the support they provide survivors, as well as the culture of hope created through their various events and fundraisers.

With nearly 100 types of sarcoma accounting for only 1% of the newly diagnosed cancers each year, there are limited resources dedicated to finding a cure. Treatment often includes intense chemotherapy regimens and invasive surgeries to remove the tumor, highlighting the need to understand the biology of these cancers and develop more effective treatments. In FY17, the PRCRP funded three sarcoma-related research projects totaling $1.8M, and this type of rare cancer continues to be of interest to the program. The PRCRP has accepted proposals for sarcoma under the Topic Area of “Cancer in children, adolescents, and young adults.” Rein in Sarcoma nominated Nate as a consumer reviewer for PRCRP, and in 2018, he served on a peer review panel. As a consumer reviewer, he felt the full commitment of the scientific community to the needs of patients and survivors. Nate also understands, as a survivor of a rare metastatic cancer, the importance of fighting for the “little guy.”
Elizabeth Naylor – When Cancer Doesn’t Care About Your Plans

Elizabeth Naylor was just 30 years old when a softball-sized tumor was discovered in her chest. She had a husband, a 2-year old daughter, and plans of buying a new home in Boston. But cancer did not care about her plans. On October 16, 2009, Elizabeth was diagnosed with primary mediastinal diffuse large B-cell lymphoma, one of the many subtypes of non-Hodgkin’s lymphoma. What started as a nagging cough and chest pain quickly became a life-changing diagnosis.

Elizabeth’s doctors were confident that traditional chemotherapy would work well, and she underwent treatment with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP). However, after only two rounds of R-CHOP, it was evident that the treatment was not working. The tumor had grown and pushed through Elizabeth’s chest cavity in just a few weeks. In November 2009, she began a second type of chemotherapy – rituximab, ifosfamide, carboplatin, and etoposide phosphate (R-ICE) – which required 4 days in the hospital with each treatment. Her doctors in Boston had planned for four rounds of R-ICE plus radiation and then a transplant of her own stem cells. Heartbreakingly, after two rounds of R-ICE, Elizabeth’s condition significantly worsened.

Refusing to give up hope, Elizabeth learned of several clinical trials ongoing at the National Institutes of Health (NIH) in Bethesda and found an experimental protocol that was appropriate for her cancer. Under the hopeful guidance of the NIH lymphoma team, she enrolled in the clinical trial to begin a third type of chemotherapy – etoposide, cyclophosphamide, doxorubicin, vincristine, prednisone, plus rituximab (EPOCH+R). Elizabeth and her husband traveled from Boston to Bethesda in order for her to participate in the trial, which required 72 hours of continuous treatment for each round of EPOCH+R. Elizabeth had to keep up with pain pills, steroids, and anti-nausea medication while her husband made the 400-mile drive each way. Initially, the NIH team planned for Elizabeth to undergo four rounds of EPOCH+R. However, on their third trip to Bethesda, Elizabeth and her husband learned that not only was the tumor in her chest not shrinking, but a large tumor encasing her right kidney had developed as well. Things had gone from very bad to nearly hopeless.

Elizabeth was now faced with the terrifying possibility that she only had 3 months to live. Her doctors felt that her only chance of survival would be an allogenic stem cell transplant. Luckily, Elizabeth’s sister was a match, but her doctors in Boston weren’t confident that she could survive the procedure. Thinking of her 2-year old daughter, Grace, Elizabeth kept fighting. She and her husband decided to move to Maryland for 100 days so that she could enroll in a second clinical trial at NIH and undergo the allogenic stem cell transplant. The donor cells from her sister began attacking the cancer from the beginning, but around day 75, they also began attacking her skin and lower intestine. Graft-versus-host disease took a toll on Elizabeth’s body and she was hospitalized for several days. Despite the setbacks, Elizabeth improved, and after 100 days she and her family were able to move back to Boston under careful monitoring instructions.

Elizabeth is now 2.5 years in remission, with no signs of cancer activity anywhere in her body. She describes her experience as a participant in the clinical trials as not only life-saving, but essential to helping her doctors learn what could work for countless other patients in the future. Having worked so closely with her healthcare team, Elizabeth saw firsthand that they care deeply about each patient and are truly dedicating their lives to improving the outcomes for all of those living with lymphoma.

Over the last 9 years, she has been involved with The Leukemia and Lymphoma Society and The Lymphoma Research Foundation. She joined the PRCRP as an ad hoc reviewer for programmatic review in 2019 as a way to give a bigger voice to consumer advocates in the research community. By sharing her cancer story, Elizabeth hopes to inspire patients and other consumer advocates to keep speaking and sharing their stories.
Cancer Care Spectrum

The Cancer Care Spectrum (CCS) is a tool used by PRCRP to categorize the types of research funded by the program: biology/etiology, prevention, diagnosis/detection, prognosis, treatment, and survivorship. The CCS allows the program to assess the portfolio, identify gaps in research, and determine potential areas to modify investment. The CCS also helps with visualizing the state of the science for each of the topic areas funded by PRCRP.
Dr. Haining Yang Establishes Herself as an Independent Investigator and Enhances Our Knowledge of Early Stages of Mesothelioma Development

Haining Yang, M.D., Ph.D., University of Hawaii

Topic Area: Mesothelioma

Mechanism: FY12 Career Development Award; FY15 Idea Award with Special Focus; FY15 Translational Team Science Award

Mesothelioma is a rare and aggressive cancer with few treatment options. Service members, Veterans, and their families are at risk for developing mesothelioma due to asbestos exposure during deployment. However, the mechanisms of how asbestos exposure leads to mesothelioma are still unclear. There is an urgent need to understand the early stages of mesothelioma development, which could lead to improved diagnostic and prevention methods.

Dr. Haining Yang has been actively involved in mesothelioma research since 2003, when she joined the lab of Dr. Michele Carbone as a post-doctoral fellow. As an independent researcher, Dr. Yang continued her research into mesothelioma and was awarded a FY12 Career Development Award to study whether mutations in the tumor suppressor BAP1 influence secretion of pro-inflammatory proteins following asbestos exposure. In vitro studies demonstrated that silencing BAP1 in either mesothelial cells or macrophages, a type of immune cell, resulted in increased cytokine secretion. Furthermore, the mesothelial cells with silenced BAP1 were much more resistant to cell death following asbestos exposure, suggesting a higher number of asbestos-damaged cells survived, increasing the risk that some of them could grow into a malignancy. Animal studies confirmed these findings; BAP1 knockout mice had a higher incidence of mesothelioma development following injection a small amount of asbestos (36%) compared to wildtype mice (8%). These findings suggest that even minimal exposure to asbestos can significantly increase the risk of mesothelioma in genetically predisposed individuals. During this award, Dr. Yang was promoted to tenured Associate Professor.

The results from her FY12 project were leveraged to obtain two FY15 PRCRP awards. The first, an Idea Award with Special Focus, continues to focus on identifying genetic mutations that predispose individuals to mesothelioma. Whole exome sequencing of patients with hereditary mesothelioma was performed to identify susceptibility variants. Mutations of several genes have been discovered and the mechanisms are being studied. Dr. Yang is currently performing long-term animal studies to understand how these genetic mutations contribute to mesothelioma development in vivo. The results of this project will contribute to developing novel screening tools for mesothelioma detection and targeted therapeutics to improve mesothelioma treatment.

Dr. Yang’s second FY15 award is an ambitious Translational Team Science Award. Working with Dr. Michele Carbone at University of Hawaii, Dr. Harvey Pass at New York University School of Medicine, Dr. Justyna Fert-Bober at Cedars-Sinai Medical Center, and Dr. Tak Mak at Toronto’s University Health Network, they are continuing to study the role of HMGB1 in mesothelioma development. Dr. Yang hypothesized that HMGB1 working hypothesis for mesothelioma carcinogenesis. Asbestos causes necrotic human mesothelial cell death, leading to the release of HMGB1 into the extracellular space. As a key mediator of inflammation, HMGB1 can induce activation of Nalp3 inflammasome and subsequent IL-1β secretion, as well as eliciting macrophage accumulation and triggering the inflammatory response and TNF-α secretion, which increases the survival of asbestos-damaged mesothelial cells. This allows key genetic alterations to accumulate within mesothelial cells that sustain asbestos-induced DNA damage, leading to the initiation of mesothelioma.
expression in blood is a potential biomarker for detection of mesothelioma at early stages of the disease. This is important, because early disease detection is associated with better responses to therapy and prolonged survival. However, there are different forms of HMGB1, and it is currently unknown if specific isoforms of HMGB1 are associated with mesothelioma. Dr. Yang and her team have developed HMGB1 knockout mouse models and are currently performing long-term studies assessing whether HMGB1 expression is critical for malignant mesothelioma following asbestos exposure. The second goal of this project is to develop a clinical blood-based test for early detection of mesothelioma. If successful, clinicians will be able to identify asbestos-exposed individuals and monitor those with high levels of HMGB1 for early signs of mesothelioma. Ultimately, this test could be used to screen populations, such as Veterans, known to be at a high risk for mesothelioma.


A Big Data Approach to Identifying Novel Targets in Gastric Cancer

Rehan Akbani, Ph.D., University of Texas M.D. Anderson Cancer Center

Topic Area: Stomach Cancer

Mechanism: FY15 Career Development Award

Due to past and present deployments, United States Service members and Veterans may have an increased risk of developing stomach cancer, especially if diagnosed with Helicobacter pylori, the causative bacteria in ulcer development and gastric cancer (GC). The cause of GC is largely attributed to diet, geography, and infections.

In FY15, Dr. Rehan Akbani was awarded a Career Development Award to initiate an exploratory, big data project that comparatively analyzed GC against 32 other cancers (in The Cancer Genome Atlas data set), including colorectal cancer, adeno-esophageal cancer, and squamous esophageal cancer, to elucidate potential therapy targets.1 With PRCRP support, his team assessed different tumors’ immune landscapes with the goal of discovering novel and specific therapeutic targets for GC. By differentiating between GC and other gastrointestinal-related cancers, Dr. Akbani is helping to open the door for precision medicine. His team discovered that GC tumors have comparatively low activity of genes associated with wound healing, which may exacerbate damage caused by Helicobacter pylori and the tumor itself. GC tumors also displayed high activity of transforming growth factor-beta (TGF-ß) pathway mRNA expression, which is a key signaling pathway involved in modulating many cell processes, including cell growth, proliferation, and death, thereby affected immune activation and/or suppression. The modulation of the TGF-ß pathway could explain the GC tumors’ initiation and growth. GC tumors also displayed higher KRAS, HRAS, and NRAS gene expression (which contributes to the regulation of cell proliferation and differentiation) compared to other gastrointestinal-related cancers. This immune landscape may elucidate tumor growth and suggests some patients may potentially benefit from RAS-targeting treatment. Dr. Akbani also reported relatively high activity of macrophage regulation and lymphocyte infiltration (immune cells that help the body identify and fight foreign cells in the body) in GC tumors, which supports the feasibility of utilizing immunotherapy treatment options. Through comparative analysis, Dr. Akbani’s team also found GC tumors frequently exhibit alterations in pathways involved in repairing DNA damage, including direct damage reversal, mismatch, and homology-dependent repair pathways. Further studies may help determine whether targeting these DNA repair pathways is a possible treatment option.

These findings have been reported in six published articles, which have already accumulated over 100 citations. Dr. Akbani’s work has and will continue to guide GC screening and therapeutic research toward a more focused, targeted approach. His team continues to analyze data and validate findings with special focus on identifying sub-groups of GC. Dr. Akbani plans to better identify distinct characteristics of GC subgroups in hopes of enabling researchers and clinicians to more effectively and efficiently diagnose and treat GC, thus improving patients’ lives.

Development of Novel Imaging Methods for Detecting Glioblastoma Multiforme

Jason M. Warram, Ph.D., University of Alabama Birmingham

Topic Area: Brain Cancers

Mechanism: FY17 Idea Award with Special Focus

Glioblastoma multiforme (GBM) is the most common brain tumor that occurs in adults, yet the 5-year survival rate is only 5%, with the majority of patients surviving less than 14 months after diagnosis. It is a rapidly growing, aggressive tumor that grows diffusely into neighboring areas of the brain. Exposure to ionizing radiation is the main external risk factor associated with GBM, and individuals, particularly Service members, exposed to nuclear weapons testing or other types of ionizing radiation are at an increased risk of developing GBM compared to the general population. There are known survival benefits associated with surgical removal of the GBM tumor. However, the diffuse growth of the tumor makes it difficult for a surgeon to clearly distinguish tumor cells from adjacent, healthy cells. As a result, GBM cells remain in the brain post-surgery, leading to tumor recurrence and the death of the patient. Therefore, there is an urgent need for novel tools that improve tumor detection and the prognosis for individuals diagnosed with GBM.

Dr. Warram received an FY17 Idea Award with Special Focus to develop and test, in preclinical models, an imaging probe that is both sensitive and specific in distinguishing GBM tissue from healthy tissue. The novel imaging probe will target a cell-surface marker, matrix metalloproteinase 14 (MMP-14) that is expressed to a much greater degree in GBM cells than in healthy cells. Upon binding to its target, a dual-modality fluorescent tag will be activated. This tag will be detectable by both positron emission tomography (PET) to allow for pre-operative assessment of tumor burden and localization, and by near infrared fluorescence (NIRF) imaging to allow for real-time surgical guidance in distinguishing tumor cells from healthy cells. Once developed, the use of this probe will be validated in mouse models of GBM. The successful development of this innovative tool will provide a crucial foundation to address a critical gap in managing GBM patient care.

Schematic representation of the MMP-14 imaging probe design (top panel) and mechanism of action to detect GBM cells. MMP-14 expressed on GBM cells activates the NIRF signal of the probe and allows the probe to bind to the GBM cells (bottom left panel), which can be identified pre-operatively through PET and during surgery through real-time NIRF imaging. The NIRF signal remains off and the probe is not retained on healthy brain cells, which have very low expression of MMP-14 (bottom right panel), thus enabling highly sensitive, specific detection of GBM for surgical removal.
Development of Novel Noninvasive Tests for Prognostic Predictions for Bladder Cancer

Vinata Lokeshwar, Ph.D., Augusta University

Topic Area: Bladder Cancer

Mechanism: FY17 Idea Award with Special Focus

Bladder cancer (BC) is a carcinogen-driven cancer that arises in the inner lining of the bladder and is the fourth most common cancer among US military personnel. The predominant environmental risk factor attributed to BC development is smoking cigarettes; 68% of military personnel are active or past smokers. BC tumors are classified as either low-grade or high grade. High-grade tumors are aggressive because they are more likely to invade the muscle surrounding the bladder and become muscle-invasive BC (MIBC). If the tumors are not MIBC, the tumor is surgically resected. However, despite surgical resection of the tumor, 50% of patients with low-grade tumors and 80% of those with high-grade tumors develop a new tumor in the bladder (recurrence) within 3 years. If the tumor is MIBC, patients undergo bladder removal surgery (cystectomy).

There are numerous challenges associated with the treatment of BC. First, because of the high risk of recurrence, BC patients are monitored regularly by cystoscopy, a painful and invasive procedure that is expensive and exposes patients to an increased risk for urinary tract infections. Furthermore, patients with resected high-grade tumors will undergo additional bladder resections after the removal of a non-MIBC tumor to confirm the non-muscle-invasive diagnosis. A second challenge is that patients with MIBC receive a 12-week course of gemcitabine plus cisplatin neoadjuvant chemotherapy (NAC) before undergoing cystectomy, but not all patients respond to this treatment. If a patient’s cancer does not respond to the treatment, then there is a danger that the cancer may grow and spread in that 12-week period prior to cystectomy. Finally, there are no approved, non-invasive biomarker tests that can detect tumor recurrence, identify tumor grade at the time of diagnosis, or predict which patients will respond to NAC treatment.

Dr. Vinata Lokeshwar received an FY17 Idea Award with Special Focus to develop and validate novel, noninvasive urine tests that could discern tumor grade, monitor for BC recurrence, and predict response to NAC. In preliminary studies, Dr. Lokeshwar’s team identified a specific variant of an infrequently studied enzyme, HYAL4-V1 (V1), as a promising candidate for a urine biomarker to detect BC and evaluate tumor grade with high precision and accuracy, and predict patient response to chemotherapy. Dr. Lokeshwar is using the award to evaluate V1-based urine tests for their diagnostic and predictive capabilities at various stages of BC. The V1-based tests are also being evaluated for their ability to detect BC recurrence. She is also investigating whether V1 promotes BC development, spread (metastasis), and resistance to chemotherapy. A successful V1-based urine test would reduce the patient morbidity and costs associated with monitoring for BC recurrence and additional bladder resections. Additionally, if accurate for predicting response to NAC, V1-based urine tests could inform clinicians as to whether a patient should receive NAC treatment or forego chemotherapy and pursue immediate cystectomy. If V1 and its effectors are established as molecular drivers of malignant disease and chemoresistance, this could allow for the development of V1-based treatments for BC.

Validated urine tests would meet a critical need to reduce BC-related morbidity and healthcare costs, not just for the general public, but particularly for US service members, retirees, and their families.
Oncolytic Immunotherapy for Diffuse Intrinsic Pontine Gliomas (DIPG)

Marta M. Alonso, Ph.D., (left) University Clinic of Navarra (Spain)
Candelaria Gomez-Manzano, M.D. (middle); Juan Fueyo, M.D., (right)
University of Texas MD Anderson Cancer Center

Topic Area: Pediatric Brain Tumors
Mechanism: FY16 Translational Team Science Award

DIPG is an aggressive, lethal form of pediatric brain tumor for which the 5-year survival rate is nearly zero. DIPG arises from a class of cells in the brain called glia that perform support and protection roles for neurons. These tumors start in the part of the brain stem called the pons, which controls crucial bodily functions like heart rate, blood pressure, and breathing. The sensitive region of the brain where DIPG grows and the diffuse nature of tumor growth make surgical removal of DIPG tumors impossible. Until recently, surgeons would not even collect biopsies of DIPG tumors, because the risk of injury to the patient was too high, and the analysis of the biopsy could not inform therapeutic approaches. Therefore, little is known about what causes DIPG, how tumors progress, or how to effectively treat the tumors. For these reasons, little progress has been made in the treatment of DIPG.

Because genetic information about DIPG is largely unknown, the possibility of generating efficacious personalized medicine is currently unrealistic. However, advances in immunotherapy, including the use of viruses designed to attack and kill tumor cells (e.g., oncolytic viruses) and the use of therapeutics that encourage a patient’s own immune system (i.e., immunotherapy) to target and reverse tumor growth are exciting approaches that are already actionable in other cancer types. Dr. Marta Alonso and her colleagues, Dr. Candelaria Gomez-Manzano and Dr. Juan Fueyo, are hopeful that their work, funded by a FY16 Translational Team Science Award, will provide a much needed spark in the DIPG field.

Prior to the current award, Drs. Alonso, Fueyo, and Gomez-Manzano developed and tested in Phase I/II clinical trials the oncolytic virus, Delta-24-RGD, in adult glioma patients with recurring tumors. Among the exciting preliminary results of these trials was the observation that the treatment resulted in no significant side effects in patients and that administering the virus resulted in a complete response to therapy in some patients. However, because pediatric brain tumors like DIPG respond differently to therapy than adult tumors, the Dr. Alonso and her colleagues are currently developing and testing new oncolytic viruses specific for the treatment of DIPG tumors.

Dr. Alonso has also made strong advances in testing the antitumor effects of an oncolytic virus designed to target DIPG, Delta-24-ACT. Over the last year, she used a mouse model of DIPG to show that the newly constructed virus is able to infect mouse DIPG cell lines, replicate, and kill the tumor cells. Preliminary studies in mice show that virus administered directly to DIPG cells in mouse brains is also able to infect the cells and replicate, which are important indicators that the virus would be effective in a human brain. Further studies evaluating the ability of Delta-24-ACT to selectively kill DIPG cells in mouse models of the disease are ongoing. Also in the upcoming year, the team will develop and test additional viruses that not only target and kill DIPG cells, but are also able to stimulate a robust immune response to increase efficiency of the oncolytic virus. These are important preclinical studies that are necessary to lay the foundation for future clinical trials in humans.

This project has gone from the bench to the clinic and back to the bench. The novel biological therapeutic tools being developed under this award have the potential to drastically improve the prognosis of children with brain tumors without resulting in unacceptable toxicity. Upon completion of this project, Drs. Alonso, Fueyo, and Gomez-Manzano expect to have sufficient preclinical data to initiate a radically innovative clinical trial for DIPG patients based on local delivery of an oncolytic virus, a similar strategy to the one used in adult glioma clinical trials, combined with an immune boosting strategy. The success of any subsequent clinical trial in improving the outlook for children diagnosed with DIPG would provide a tremendous step toward alleviating the burden of such a diagnosis on families, particularly military families and the adverse impact such a diagnosis has on mission readiness.
Developing advanced therapies that are more effective and less toxic is crucial to improving the quality of life of cancer patients. Immunotherapy is a treatment that utilizes the body’s immune system to induce an anti-tumor response and fight off cancer cells effectively while potentially decreasing toxicity. A major problem with immunotherapy is non-responding patients, or patients who respond initially and then develop resistance.

The most common type of head and neck cancer (HNC) is head and neck squamous cell carcinoma (HNSCC), which can arise in the oral cavity, nasal cavity/paranasal sinus, larynx, hypopharynx, and oropharynx. Globally, HNC accounts for approximately 500,000 cases annually. In the United States, about 3% of all cancers are HNC, with approximately 63,000 Americans developing head and neck malignancies annually. Overall, HNC is more commonly seen in men than in women. Five-year overall survival is 40%–60%, with only a modest improvement over the past two decades despite diagnostic and therapeutic advances. HNSCC pathogenesis has historically been associated with tobacco and alcohol use, but an increasing proportion of oropharyngeal HNC is driven by oncogenic human papillomavirus (HPV). HNSCC is associated with a fundamental failure of immune surveillance, where tumor cells have escaped recognition and lysis by the cytotoxic T lymphocytes (CTLs) of adaptive immunity. The efficacy of immunotherapy in the treatment of cancer relies on the capability of the therapy to enhance the cytolytic activity/functionality of tumor-specific T cells, increase their migration into the tumor, and maintain their functionality in an immunosuppressive tumor microenvironment. Improving the ability of the T cells to infiltrate the tumor and to function in the hostile tumor microenvironment remains the greatest challenge of immunotherapies in addition to the development of resistance to the therapy.

Dr. Conforti, with partnering PIs, Dr. Wise-Draper, Dr. David Hildeman, and Dr. Janssen, and their collaborators Dr. Qualtieri and Dr. Butler, received funding in FY16 through the Translational Team Science Award, to understand the ionic mechanisms that mediate the response/resistance of HNSCC patients to programmed cell death protein 1 (PD1) therapy. The team postulated that PD1 therapy increases the effect of ionized calcium (Ca2+) flow in CTLs. The failure to improve ion channel function can lead to resistance. Additionally, the team is interested in identifying whether the adenosine receptor checkpoint and/or CTLs surface receptor’s mediated complementary immune suppressive mechanisms will lead to PD1 therapy resistance. The team is assessing the activity and surface markers of CTLs of PD1-treated HNSCC patients in order to produce clinical and pathological data to determine the overall effect of PD1 on CTLs cells in vitro. The investigative team is also developing patient derived xenograft mice for the assessment of PD1 and CTL therapies. The selection of implanted tumors has been completed and the treatment of mice is underway. These experiments are intended to discover a potential feedback loop between these regulatory mechanisms. These studies are also designed to identify novel pathways in PD1 resistance as well as developing novel pre-clinical mouse models.

Identification of a Novel Therapeutic Target for the Treatment of Chronic Lymphocytic Leukemia (CLL)  

Rosa Lapalombella, Ph.D., The Ohio State University  
Topic Area: Blood Cancers  
Mechanism: FY14 Career Development Award

CLL is a type of cancer in which the bone marrow produces too many white blood cells. It is the most common form of adult leukemia in the United States. Veterans have a higher incidence of CLL than the general population due to exposure to herbicide defoliants used in the Vietnam War. There is also some evidence that exposure to these defoliants led to development of a more aggressive form of CLL, and that the exposure of fathers also led to an increased incidence of leukemia in their children.1 Recent advances in the treatment of CLL have led to improvements in managing and treating this disease; however, patients eventually relapse. Consequently, there is a need to develop new CLL therapies.

Exportin (XPO1) is a cellular protein that mediates the export of various proteins and RNAs from the nucleus. XPO1 is overexpressed in most hematologic malignancies, including CLL, where XPO1 overexpression correlates with resistance to therapy and poor prognosis. The overexpression of XPO1 leads to the development of CLL through mislocalization of tumor suppressors, such as p53, preventing their activity and thereby potentially disrupting apoptosis or cell death. The mislocalization of these tumor suppressor proteins causes a disruption in the cellular microenvironment, as demonstrated by Dr. Rosa Lapalombella of Ohio State University. Dr. Lapalombella validated the therapeutic potential of XPO-1 as a novel drug target by demonstrating that inhibiting XPO1 nuclear export selectively killed CLL cells in culture as well as slowing disease progression and increasing survival in a mouse model of CLL.

Through her FY14 Career Development Award, Dr. Lapalombella built on her earlier efforts and investigated the role of XPO1 and previously-described XPO1 mutations in CLL. CLL B-cell lines overexpressing either wild-type XPO1 or a mutated form of XPO1 were generated for the investigation. Mutant XPO1 cell lines displayed a growth rate that was higher than the wild-type parental cell lines. Dr. Lapalombella and her team utilized CRISPR/cas9-mediated homologous recombination. (CRISPR is a genetic engineering method that uses short repetitive DNA sequences and associated proteins to edit genes.) Dr. Lapalombella’s team generated CLL B-cell lines that expressed either a single copy of wildtype XPO1 or one of two XPO1 mutations. The cell lines expressing the wild-type XPO1 survived, but neither mutant cell line was viable, suggesting that a certain level of wild-type XPO1 is essential to cellular health. Dr. Lapalombella’s team engineered additional cell lines to allow them to examine XPO1 wild-type and mutant XPO1 protein-RNA and protein-protein interactions. Her research team also generated a series of transgenic mice overexpressing these proteins.

These findings and the tools created in this work laid the groundwork for Dr. Lapalombella and her collaborators to translate this research into the clinic to begin testing of this new class of drugs to treat CLL.2 Dr. Lapalombella’s Career Development Award acted as a springboard, aiding her progression in her career and resulting in two publications and follow-on funding to continue her research. Through five separate follow-on grants, she has continued to develop CLL animal models and has shown the efficacy of XPO1 as a therapeutic target for CLL. Her work has culminated in a Phase I drug combination study of the selective XPO1 inhibitors, selinexor, and ibrutinib (a common B-cell cancer therapeutic) in CLL patients, which is now ongoing.3 Dr. Lapalombella is continuing to use these tools to further develop the field and, potentially, the next generation of XPO1 inhibitors.4 The implications of the findings of the current study may impact our ability to detect, diagnose, and treat CLL.

3 https://clinicaltrials.gov/ct2/show/NCT02303392?term=selinexor+ibrutinib&rank=1
Deletion of LSP1 Improves Liver Cancer Response to Sorafenib

George Michalopoulos, Ph.D., University of Pittsburgh

Topic Area: Liver Cancer

Mechanism: FY16 Idea Award with Special Focus

Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer and has been on the rise in the United States over the last 30 years, partially due to consumption of the standard American diet, which is high in sugar and fat.¹ Military members are at an even greater risk of developing HCC due to their exposure to pesticides, infections, and liver toxins, such as Agent Orange, Hepatitis B/C, and polychlorinated biphenyls.² Current treatments for HCC are largely limited to chemotherapy, such as Sorafenib, but it is only effective in about 50% of patients. Dr. George Michalopoulos at the University of Pittsburgh studies the way HCC develops and progresses in hopes of designing new treatment options for this devastating disease that claims the lives of over 29,000 patients in the United States each year. With the support of a FY16 Idea Award with Special Focus, Dr. Michalopoulos and his team have made significant advances in understanding how a gene called Leukocyte-specific protein-1 (LSP1) promotes HCC tumor cell growth, and that it may be the key to understanding why Sorafenib treatment is ineffective in many patients. In a recent paper published in the American Journal of Pathology, Dr. Michalopoulos used cellular and animal models of HCC to show that LSP1 deletion improves HCC tumor response to Sorafenib treatment, and also identified the mechanism behind how LSP1 interferes with the treatment.³ These results suggest that patients with HCC will respond more effectively to Sorafenib treatment if their tumor is LSP1-negative. Dr. Michalopoulos is currently designing diagnostic tests that can detect LSP1 deletions, in the hopes of identifying which patients would be the most responsive to, and benefit from, treatment with chemotherapeutics such as Sorafenib. This earlier identification of effective treatment options is key for improving prognosis of patients with HCC.

Colorectal Cancer (CRC) is the third leading cause of cancer-related deaths in the United States. It is the third most common cancer in men and women. In the US Veteran population, CRC represents 9% of all malignancies. The 5-year survival rate of patients diagnosed with early-stage colon cancer is 90%, compared with less than 20% for patients diagnosed with advanced stage IV disease. While early stages of CRC are highly curable by surgical resection, the prognosis of patients with metastatic disease remains grave. Promising targeted CRC therapies, including monoclonal antibodies against epidermal growth factor receptor (EGFR), have resulted in significant improvement of overall survival in patients with metastatic disease; however, the success is limited due to resistance.

Dr. Frank, Dr. Lian, and Dr. Ng were funded with a FY16 Translational Team Science Award to develop novel anti-cancer agents to overcome therapeutic resistance in patients with metastatic CRC. This FY16 funded project will examine whether expression levels of a known multidrug resistance mediator, ABCB5, correlate to clinical outcomes in patients treated with CRC targeted therapies. ABCB5 is a plasma membrane protein and human P-glycoprotein family member, shown to be highly overexpressed by cancer stem cells in diverse human malignancies. ABCB5 is associated with clinical tumor progression, therapeutic resistance, and recurrence in patients with cancer. ABCB5 is expressed in CRC, where it mediates drug resistance to the main chemotherapeutic agent 5-FU.

To improve the clinical outcomes of CRC patients, the translational team will investigate whether the ABCB5/AXL signaling pathway is responsible for emergence of resistance to EGFR-targeting therapies in CRC. In addition, the research team aims to find out whether specific targeting of ABCB5/AXL signaling pathway through monoclonal antibody-mediated ABCB5 blockade can improve clinical outcomes in CRC patients with advanced disease. Furthermore, the research team plans to investigate whether blocking ABCB5 can improve the longevity of these therapies in preclinical models. These experimental approaches will pave the way toward the development of an investigational new drug that can facilitate further studies and inform the design of future clinical trials in patients.

### Survivorship and Continuity

The goal of cancer research is to ultimately improve the lives of those who have received the devastating diagnosis of cancer. From FY09-FY18, the PRCRP has invested $339.8M in cancer research with the goal of decreasing the burden of cancer on Service members, Veterans, their beneficiaries, and the American public. The advances that PRCRP-funded investigators make in the areas of cancer biology, prevention, diagnosis, prognosis, and treatment are making a difference when it comes to impacting cancer survivorship and quality of life. In addition to the research highlighted throughout the Program Book, below are additional examples of PRCRP-funded projects that are changing the field across the Cancer Care Spectrum.

<table>
<thead>
<tr>
<th>Fiscal Year</th>
<th>PI Name(s)</th>
<th>Award Mechanism</th>
<th>Overview</th>
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<tbody>
<tr>
<td>2011</td>
<td>Yue Wei, Ph.D., M.D. Anderson Cancer Center</td>
<td>Discovery Award</td>
<td>This project focused on the impact of deregulation of Toll-like receptor 2 (TLR2) and histone demethylase JMJD3 in myelodysplastic syndrome (MDS). Results from this study lead to the development of a Phase I/II clinical trial studying the efficacy of a TLR2 inhibitor (OPN305) in treating patients with MDS.</td>
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<td>2012</td>
<td>Sunitha Nagrath, Ph.D., M.E. University of Michigan</td>
<td>Career Development Award</td>
<td>The goal of Dr. Nagrath’s project was to develop a microfluidic cell sorting device that could isolate and detect circulating tumor cells (CTCs). Though her PRCRP project focused on detection of pancreatic cancer CTCs, she has since demonstrated this method can be applied to a variety of cancer types.</td>
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<td>2013</td>
<td>Rosa Lapalombella, Ph.D. The Ohio State University</td>
<td>Career Development Award</td>
<td>Dr. Lapalombella’s project studying the overexpression of nuclear export protein (XPO1) in CLL led to a Phase I/II clinical trial with XPO1 inhibitor selinexor.</td>
</tr>
<tr>
<td>2014</td>
<td>Maureen Su, M.D. University of North Carolina - Chapel Hill</td>
<td>Career Development Award</td>
<td>The goal of this project was to develop an antibody therapy that would increase the frequency of melanoma-targeting T cells and thus enhance the effect of immunological checkpoint inhibitors. In mouse models of melanoma, anti-RANKL (denosumab), has a synergistic effect with checkpoint inhibitors anti-CTLA4 and anti-PD1 in decreasing tumor growth and prolonging survival. The results of this project informed the development of a Phase II clinical trial in melanoma patients using denosumab in combination with anti-PD1 immunotherapy.</td>
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<tr>
<td>2014</td>
<td>Gregory Friedman, M.D. University of Alabama at Birmingham</td>
<td>Career Development Award</td>
<td>Dr. Friedman is using oncolytic herpes simplex virus (oHSV) to selectively infect and kill medulloblastoma, an aggressive pediatric brain cancer. Pre-clinical studies have shown that intraventricular delivery of oHSV is safe and effective in targeting brain tumors This work will inform the design of Phase I clinical trials for pediatric brain tumors.</td>
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**FY09-FY18 Outcomes:**

- Employment/ Promotions: 62
- Funding Obtained: 165
- Patents (Including Provisional): 42
- Publications: 670
- Presentations: 942
- Clinical Trials: 43
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