CDMRP
Department of Defense

CONGRESSIONALLY DIRECTED MEDICAL RESEARCH PROGRAMS

2021
Annual Report

US Army Medical Research and Development Command

LETTER FROM THE DIRECTOR

Dear Consumer Advocates, Researchers, Stakeholders, Military Members, and Veterans,

The Congressionally Directed Medical Research Programs (CDMRP) is pleased to present the 2021 Annual Report. CDMRP-supported research focuses on impactful innovations and advances in health care for our Service Members, Veterans, their families, and the American public. This has been a busy year, in which the CDMRP managed 36 distinct Congressional Special Interest research programs, responded to a number of external reviews, developed exciting new research initiatives, and mitigated the challenges posed by COVID 19. CDMRP's management practices have always emphasized transparency, agility, and dedication to keeping management costs low to maximize funding available for research.

This report discusses our research successes, program funding profiles, research award information, and key advancements, including specific highlights of selected projects. We remain grateful for the participation of our partners representing consumer and non-profit organizations, federal medical research funding organizations to include the National Institutes of Health (NIH) and the U.S. Department of Veterans Affairs (VA), the medical community, academia, industry, the military, and other medical research organizations in creating and sustaining these research programs. Their contributions have been essential to our success. Finally we would like to thank Congress for their support and trust in CDMRP to manage these important programs.

Sincerely,
Colonel Sarah B. Goldman, Ph.D.
Director, CDMRP
U.S. Army Medical Research and Development Command (USAMRDC)

Department of Defense
US Army Medical Research and Development Command
Congressionally Directed Medical Research Programs
Annual Report
September 30, 2021

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U.S. ARMY

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CDMRP'S MISSION: Responsibly manage collaborative research that discovers, develops, and delivers healthcare solutions for Service Members, Veterans, and the American public

CDMRP Department of Defense

US Army Medical Research and Development Command

WHO WE ARE

The Congressionally Directed Medical Research Programs (CDMRP) is a directorate within the U.S. Army Medical Research and Development Command (USAMRDC) aligned under the Army Futures Command. In 1992, a powerful grassroots effort led by the breast cancer advocacy community resulted in a congressional appropriation of funds for breast cancer that established the CDMRP. This initiated a unique partnership among the public, Congress, researchers, and the military. After almost 30 years of growth, the CDMRP now manages 36 individual research programs focused on diseases, injuries, conditions, and Topic Areas as directed by Congress. While individual programs are unique in their focus, all of the programs managed by the CDMRP share the common goal of advancing paradigm-shifting research solutions that will lead to cures or improvements in patient care or breakthrough technologies and resources for clinical benefit.

WHAT WE DO

The CDMRP strives to transform healthcare through innovative and impactful research. The CDMRP oversees the investment of congressionally directed appropriations to support groundbreaking, high-impact, meritorious projects that target critical research gaps. CDMRP funding opportunities are publicly competed and target research across the spectrum from bench to bedside, including high-risk and high-reward studies that other agencies may not venture to fund. The CDMRP funds research that benefits the military healthcare system (to include military members, military retirees, family members, and other beneficiaries) as well as the civilian population. The CDMRP also provides program and award management support for additional core Department of Defense (DOD) medical research program areas that fund intramural and extramural research addressing critical needs in military medicine.

APPROPRIATION HISTORY

CDMRP funding is not included in the DOD's requested budget. Instead, Congress adds funding for the CDMRP to execute research programs in the annual Defense Appropriations Bill. The congressional legislation, known as the Defense Appropriations Act, details funding and intent for the CDMRP, directing specific appropriation amounts and congressional guidance for our programs. Since fiscal year 1992 (FY92), Congress has appropriated more than $17.17 billion (B) in funding targeted toward 46 congressionally directed research areas/topics managed by the CDMRP. Over the past 5 years Congress entrusted ever increasing amounts of tax payer dollars to the CDMRP with a total appropriation for FY21 of $1.5B.

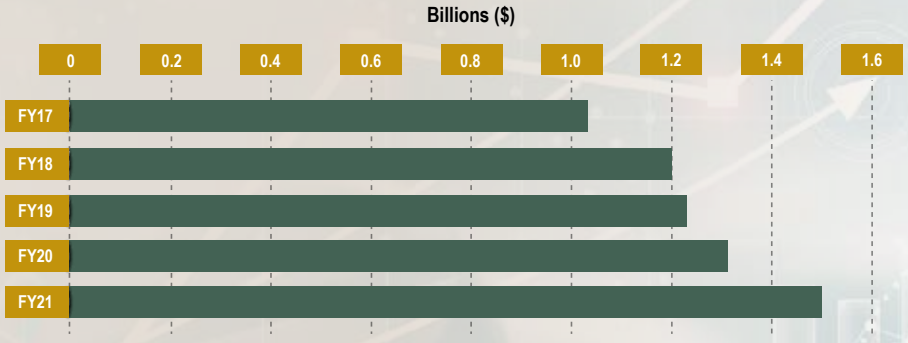


Figure 1. FY17–FY21 Research Funding

Over **$17B** Appropriated

Over **20K** Awards Funded

CDMRP'S PROCESSES

Each research program convenes a Programmatic Panel of experts to recommend a research investment strategy that addresses congressional intent and maximizes the value of research funding appropriated for a given fiscal year. At the vision setting meeting, the panel members consider the state of the science, stakeholder needs, and areas of investment by the program and other funders. The funding opportunities that solicit research applications for a given fiscal year embody this recommendation and include specific descriptions of the program's current priorities.

The CDMRP employs a two-tier process for reviewing applications submitted in response to openly competed funding opportunities. The first tier of review is scientific peer review, where scientific/technical subject matter experts and representatives of the consumer community evaluate applications based on specific review criteria outlined in the funding opportunities. In the second tier of review, the Programmatic Panel members consider the merit assessment from peer review along with additional programmatic factors, such as adherence to the intent of the award mechanism, programmatic goals, portfolio composition, relative impact, and relevance to military health, to develop a list of awards recommended for funding and approval by the Commanding General.

Once an award is made, the application enters the post-award surveillance phase, where it is monitored for technical progress and compliance with award terms and conditions. The CDMRP works with the awardee throughout the period of performance to promote successful completion of the project and accelerate progress toward a clinical impact where possible.

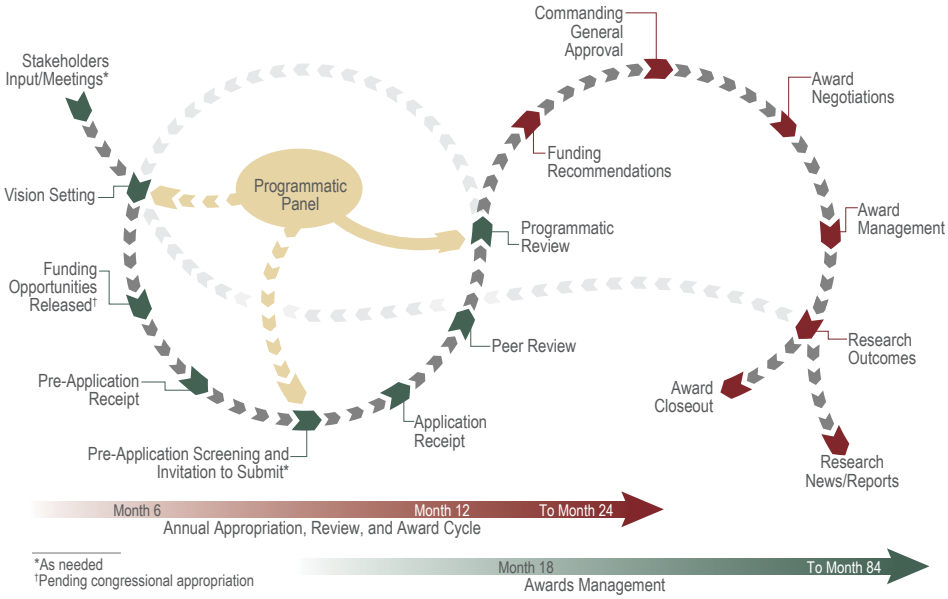


Figure 2. CDMRP Management Cycle

CONSUMER PARTNERSHIP

A hallmark of the CDMRP's process is the inclusion of consumers when setting program strategies, reviewing research applications, and making funding recommendations. Consumers have lived experience with the program-specific disease, disorder, or injury and may be a patient, survivor, family member, and/or caregiver, depending on the specific program. Consumers use their experiences to offer perspective and insight on the needs of the affected community and bring a sense of urgency to the entire process. As indicated in the adjacent figure, a large number of consumers participated on review panels in FY21 (October 2020 - September 2021). Throughout the growth of the CDMRP, consumers remain the foundation for the programs executed and managed by the CDMRP, where they serve alongside scientists, clinicians, and leading experts and have an equal voice and vote in deliberations and strategic planning.

During FY21, consumer involvement remained an integral part of the CDMRP

722 consumers served on CDMRP peer review panels

327 consumer advocacy organizations represented

83 consumers served on programmatic panels

Since the CDMRP's inception in 1992, a total of **4,135** consumers have represented their communities and organizations.

ORGANIZATION UPDATES FOR FY21

PROGRAM CHANGES IN FY21

Traumatic Brain Injury and Psychological Health Research Program (TBIPHRP)

In a significant change for FY21, the CDMRP is providing full life-cycle management of the appropriation for TBI/PH through the TBIPHRP. The FY21 TBIPHRP scope includes the prevention, diagnosis, treatment, and rehabilitation of TBI and PH and spans the research spectrum to include basic, applied, and clinical research. As part of the FY21 program cycle, a stakeholders meeting was held, with over 120 TBI and PH experts and consumers who identified critical issues and underfunded areas of TBI and PH research and care. At the FY21 Vision Setting meeting, the Programmatic Panel members developed the FY21 TBIPHRP Strategic Plan as well as FY21 TBIPHRP Investment Strategy. For more information about the TBIPHRP, see pages 80-81.

FUNDING INCREASES FOR FY21 CDMRP PROGRAMS

Fourteen CDMRP programs received increases in funding in FY21 compared to FY20. Notably, Amyotrophic Lateral Sclerosis, Bone Marrow Failure, Pancreatic Cancer, and Rare Cancers Research Programs experienced a doubling or more of their funding for FY21. Additionally, the Peer Reviewed Alcohol and Substance Abuse Disorders Research Program did not receive an appropriation in FY20, but was appropriated funds in FY21.

CDMRP Program	FY20 $M*	FY21 $M	Increase $M
Alcohol and Substance Abuse Disorders	0	4	4
Amyotrophic Lateral Sclerosis	20	40	20
Bone Marrow Failure Disease	3	7.5	4.5
Kidney Cancer	40	50	10
Lung Cancer	14	20	6
Melanoma	20	30	10
Multiple Sclerosis	16	20	4
Neurofibromatosis	15	20	5
Pancreatic Cancer	6	15	9
Peer Reviewed Cancer	110	115	5
Peer Reviewed Medical	360	370	10
Traumatic Brain Injury and Psychological Health**	165	175	10
Rare Cancers	7.5	17.5	10
Tuberous Sclerosis Complex	6	8	2

* M - Million

**For FY20 the TBIPH appropriation was managed by others with support from CDMRP as requested. In FY21 CDMRP is providing full management of this appropriation.

US GOVERNMENT ACCOUNTABILITY OFFICE (GAO) REVIEWS

CDMRP Research Program Effectiveness

In the third quarter of FY21, the CDMRP underwent a comprehensive review by the Comptroller General, as directed in the FY21 Defense Appropriations Act (HR 133). The review is focused around three main questions:

(1) To what extent does the DOD execute its annual appropriation for congressionally directed medical research?
(2) To what extent does the DOD measure its return on research investment for its CDMRP?
(3) To what extent does the DOD's CDMRP coordinate research with the National Institutes of Health (NIH) and U.S. Department of Veterans Affairs (VA)?

Results of this audit are expected to be made public in early 2022.

Underrepresented Populations in Federally-Funded Cancer Research Clinical Trials

The "Henrietta Lacks[1] Enhancing Cancer Research Act" of 2019 requires the GAO to complete a study reviewing how federal agencies address barriers to participation by individuals from underrepresented populations in federally funded cancer clinical trials.

As a result of this mandate, the GAO initiated a review of clinical research subject participation for all cancer research supported by federal biomedical research organizations, including the CDMRP. The four questions the review aims to address are:

(1) To what extent do cancer clinical trials include diverse representation?
(2) What actions have been taken to help reduce disparities in cancer clinical trial participation?
(3) What have been the challenges, if any, encountered in implementing actions to help reduce disparities in cancer clinical trial participation?
(4) What actions could help reduce disparities in cancer clinical trial participation?

Results of this multi-agency review are expected to be made public in 2022.

POLICY ON INCLUSION OF WOMEN AND MINORITIES IN CLINICAL RESEARCH

Historically, clinical research in the United States was largely focused on white, male populations, thus not accounting for any possible genetic and biomedical differences between sexes, races, and ethnicities and preventing female and minority populations from fully benefitting from clinical advances. CDMRP funding opportunities have encouraged inclusion of women and minorities in clinical trials since 2009.

In an effort to further establish appropriate representation in clinical research and in compliance with the 2019 Defense Appropriations Act (H.R. 6157), the CDMRP issued new policy and guidelines in FY21 on the inclusion of women and minorities as subjects in clinical research. The policy requires that "women and individuals from minority groups be included in all CDMRP-funded clinical research studies, unless there is a clear, justifiable rationale that it is inappropriate with respect to the health of the subjects or the purpose of the research."

This policy led to changes to FY21 funding opportunity language, application submission content, scientific review criteria, and technical reporting requirements. The CDMRP presented this policy and discussed policy execution with other agencies at two high profile meetings: the National Academies of Sciences, Engineering, and Medicine workshop on diversifying clinical trials, as well as the Vivian Pinn Symposium on Integrating Sex and Gender into Biomedical Research as a Path for Better Science and Innovation. For the complete policy and guidelines, see the "Resources and Reference Material" section under the Funding Opportunities and Forms tab on the electronic Biomedical Research Application Portal (eBRAP) website at https://eBRAP.org.

[1] Henrietta Lacks was a 31-year-old African American women being treated for cervical cancer at Johns Hopkins Hospital. In January 1951, her surgeon took a sample of her cells without her knowledge or consent for laboratory study. Normally, cancer cells taken from patients would die after a few passages but the cells taken from Mrs. Lacks amazed researchers because they just kept on dividing, providing a consistent renewable source of human cells for research. These "HeLa" cells (from the first two letters of Mrs. Lacks' first and last names) were the first human cells established in culture and have been the subject of tens of thousands of biomedical research studies in all areas of biology. The 2019-2020 legislation aimed at greater diversity in clinical research participation was named in her honor.

ACCOMPLISHMENTS AND OUTCOMES

In calendar year 2021, the CDMRP simultaneously executed two consecutive congressional appropriations (FY20 and FY21). Program staff worked in partnership with the U.S. Army Medical Research Acquisition Activity (USAMRAA), to obligate FY20 funds while establishing FY21 investment strategies. The table below highlights notable numbers from this year's efforts.

2021 Notable Numbers

Over **$1.2B** managed within 34 programs for FY20

$1.1B invested into research for FY20

12K	8K	1K
FY20 pre-applications	FY20 full applications	FY20 funded applications

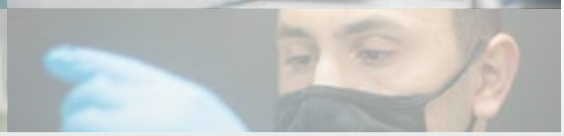
Over **$1.5B** appropriated within 36 programs for FY21

Research Results 2020-2021

1.2K publications

800 presentations

10 patents



New FY20 Research

468 projects supporting cutting-edge investigation into fundamental research relevant to critical research gaps, totaling over $402M

422 projects aimed at accelerating the movement of promising research into clinical applications, totaling over $482M

110 projects investigating patient-centered research questions, including those relevant to patient care, public health, and psychosocial outcomes, totaling over $177M

210 projects aiming to synergize scientific advancements through collaborative research opportunities, totaling over $255M

125 projects looking to foster talented new scientists and ensure a robust, multi-generational research community, totaling over $86M

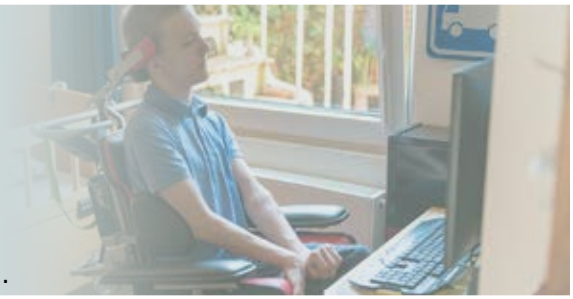
The CDMRP Impact Highlights Book published June 2021 contains numerous examples of CDMRP successes and impacts. This impressive resource is available now on the CDMRP website.

CDMRP-Funded Products Accessible to Patients Now

Consistent with CDMRP's mission to develop and deliver healthcare solutions, research funded by the CDMRP has led to development and testing of U.S. Food and Drug Administration (FDA) regulated drugs and devices as well as significant changes to clinical practice. The following list contains select examples of CDMRP-supported products that either achieved critical FDA regulatory milestones or led to important changes to clinical practice in 2020 or 2021:

The Peer Reviewed Cancer Research Program funded the preclinical research that led to the FDA-approval of **XPOVIO**® (selinexor), an orally administered blood cancer therapy that is less toxic than traditional chemotherapies.

The Peer Reviewed Medical Research Program, with continued support from the Joint Warfighter Medical Research Program, funded the development of **BIO 300**, a potential therapy to increase survival and prevent negative biological effects in persons exposed to high levels of radiation. In August 2021, the FDA granted BIO 300 Fast Track designation, thus highlighting the critical unmet medical need for development of new methods to protect against radiation exposure for our Warfighters and first responders.



The Spinal Cord Injury Research Program supported preclinical safety and efficacy studies for the **Stentrode™**, a noninvasive Brain-Computer Interface that allows participants with severe motor dysfunction or paralysis to control computers remotely with their minds. In July 2021, the FDA issued an Investigational Device Exemption to the company that produces the Stentrode in preparation for a clinical trial slated to begin in late 2021, and in November, Time magazine named the Stentrode one of the the best inventions of 2021.

The Prostate Cancer Research Program funded translational studies that contributed to the design of clinical trials that supported the FDA approval of PARP inhibitor **Rubraca**® (rucaparib). As of May 2020, Rubraca is approved for use as a metastatic prostate cancer therapy, providing a new treatment option for patients with advanced stage disease that is unresponsive to other therapy options.

The Orthotics and Prosthetics Outcomes Research Program supported the evaluation of a novel **Narrow Beam Walking Test** (NBWT) for assessing fall risk in lower limb prosthesis users that was determined to be more accurate than existing clinical balance tests. As a result, clinical, industry, and academic centers across the U.S., including several Veterans Administration Health Care Systems, have adopted the NBWT within their standard assessment battery.

MAJOR ADMINISTRATIVE INITIATIVES IN 2021

COVID-19

During the COVID-19 pandemic, the CDMRP made safety and wellness a priority, authorizing staff maximum telework flexibilities without adversely affecting execution of the CDMRP mission. All review, progress, and planning meetings transitioned to the remote environment, allowing for maximum ease of participation. The CDMRP expects to continue utilizing virtual business meetings throughout much of the FY21 program cycle.

In coordination with USAMRAA, the CDMRP also permitted flexibilities in proposal submission and award management to aid those whose operations were adversely impacted by COVID-19. Application submission deadlines incorporated the maximum time feasible for each FY20 program, and the USAMRAA permitted extensions to financial and technical reporting by award recipients. Some programs allocated a portion of their FY20 and/or FY21 funding to support critical studies by covering a portion of the unanticipated costs incurred due to the pandemic restrictions. Impacts of COVID-19 on study progress continue to be monitored.

The CDMRP demonstrated flexibility in response to the pandemic by contributing to critical efforts in COVID-related research. The Peer Reviewed Medical Research Program (PRMRP) was uniquely positioned to rapidly respond to the COVID-19 global health crisis. Leveraging two of its congressionally directed Topic Areas, "Emerging Viral Diseases" and "Respiratory Health," the PRMRP released specialized FY20 program announcements (PAs) as well as added funds to current projects with COVID-related focus. Some PRMRP-funded projects were also allowed to pivot to include COVID-19-related research if appropriate. The PRMRP invested a total of $88.3M in COVID-19 targeted research efforts (for more information please refer to pages 62-65). Other programs are responding to the COVID-19 pandemic in different ways, such as investing in understanding how COVID-19 may influence current disease conditions, placing increased focus on novel telehealth solutions, or encouraging research into psychosocial issues such as loneliness and social isolation. Additionally, the Multiple Sclerosis Research Program released three PAs in FY21 that include a Focus Area on interactions between multiple sclerosis and COVID-19.

MILITARY HEALTH SYSTEM DATA INITIATIVE

CDMRP programs support high-impact research aimed at Warfighter health and readiness. While some programs target military medical issues resulting from active-duty Service, such as injuries or conditions related to deployment, combat rehabilitation, and reintegration, all CDMRP programs relate to the general ability of the military forces to fulfill their assigned mission. Military readiness depends not only on the health of the Warfighter, but also on the health and well-being of their beneficiaries and families, all of which ultimately impact the force and the Military Health System.

Currently, the CDMRP is engaged in an ongoing effort to coordinate with the Defense Health Agency (DHA) Armed Forces Health Surveillance Branch. This initiative will provide data capturing the burden of diseases, injuries, and conditions relevant to CDMRP programs, which will help identify important issues related to the health of active-duty Service Members and their families and clarify the relevance of these programs to maintaining a ready military force.

In order to continue its mission during the COVID-19 pandemic, the CDMRP successfully conducted all business meetings virtually. The number of virtual CDMRP meetings, as well as virtual speaking engagements held by other organizations that the CDMRP participated in from September 2020 - September 2021 is indicated below.

CROSS-AGENCY DATA SHARING

In 2021, the CDMRP and the NIH continued to partner on an interagency data-sharing initiative to strengthen efforts to prevent unnecessary duplication of funding for biomedical research by federal agencies. The CDMRP entered into a Memorandum of Agreement (MOA) with the NIH in 2019 to share pre-award application information with other federal funders to allow for greater visibility and better inform funding decisions. By utilizing a central repository managed by the NIH to store, access, and search proposal and award data, these agencies can now more efficiently share information. Additionally, new automated tools available within the shared database allow for identification of similarities between projects to help assess and flag duplicative research. This exciting initiative provides scientific staff across multiple federal agencies (including the Department of Health and Human Services, the VA, and the DOD) real-time data on incoming research applications and current funding statuses, which enables them to realize cost savings by identifying duplication and streamlining the research administration process. This data-sharing initiative, which has been years in the making, has the potential to further increase collaboration and increase efficiencies as additional capabilities are being explored.

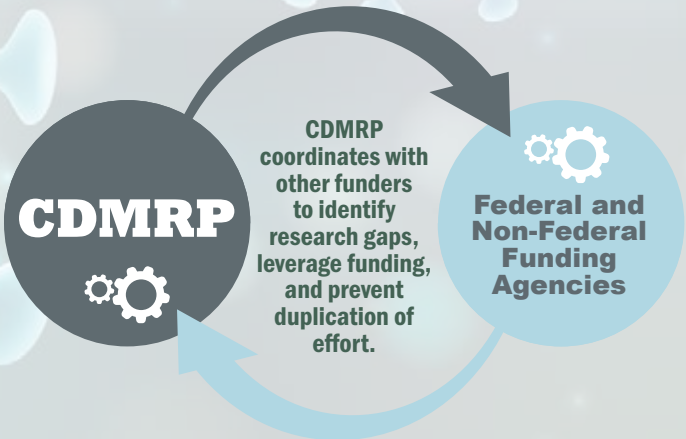
INTERAGENCY COLLABORATIONS

The CDMRP and other biomedical research funding programs communicate and actively coordinate to identify gaps, strategically plan investments, and prevent duplication of effort. CDMRP representatives participate in conferences, workshops, and working groups comprised of federal and non-federal participants to ensure proper coordination across agencies that aligns with public interests. Notable collaboration opportunities this year include:

- DHA-sponsored Review and Analysis (R&A) meetings, in which the NIH, VA, and other stakeholders gather to review the current CDMRP research portfolios
- Joint DOD-VA Gulf War State of the Science conference
- National Academy of Sciences, Engineering, and Medicine's Accelerating Progress in TBI Research and Care workshop

In 2021, the Vision Research Program and the National Eye Institute renewed the Vision Research Collaborative, which provides additional funding opportunities for meritorious VRP proposals, expands the scope of research supported by the NEI, and enhances support for high quality projects addressing critical gaps in civilian and military vision research. CDMRP programs also participate in shared portfolio coding and tracking processes with federal and non-federal funding agencies to more effectively map the research funding landscape.

Finally, investigators and programmatic staff from the VA, the NIH, Department of Health and Human Services, and other federal and non-federal funding agencies serve as reviewers on CDMRP peer and programmatic review panels. Over 70 individuals representing other federal organizations served on the FY20/FY21 Programmatic Panels during 2021. These panel members bring both their expert knowledge in the field and their organization's funding strategy to help shape the future of CDMRP investments.



OUR PROGRAMS

The 36 research programs highlighted in this section share many common features, yet each program is unique and emphasizes the specific needs of the research and advocacy communities. These programs are detailed on the following pages.

ALCOHOL AND SUBSTANCE ABUSE DISORDERS RESEARCH PROGRAM

Vision: Improve the clinical outcomes of alcohol, opioid, and other substance use disorders

Mission: To explore integrated approaches to address alcohol and substance use disorders, and reduce the number of opioid and other substance use-related deaths, through multidisciplinary, team-based research efforts that translate basic knowledge into enhanced clinical pharmacological treatment protocols and enhanced quality of life for Service Members, Veterans, and the American public

PROGRAM HISTORY

The problem of alcohol and substance abuse is a growing concern among the general public, as well as military personnel and Veterans alike, even more so if accompanied by post-traumatic stress disorder (PTSD). In 2013 the Institute of Medicine (now the National Academy of Medicine) reported in Substance Use Disorders in the U.S. Armed Forces[1] that the increasing medical burden imposed on the Military Health System (MHS) by excessive alcohol use elicited their recommendation that the Department of Defense (DOD) assume leadership to ensure the consistency and quality of treatment services available to those with alcohol and substance use disorders (ASUD), given the burden of ASUD in the military. The Peer Reviewed Alcohol and Substance Abuse Disorders Research Program (ASADRP) did not receive an appropriation in Fiscal Year 2020 (FY20), but continued to manage open awards. In FY21, $4 million (M) was appropriated to the ASADRP as Congress recognized the ongoing threat posed to Warfighters and the general public by the opioid epidemic: Those who may develop an opioid dependency following an injury generally struggle with addiction. Service Members who have family members that struggle with addiction are often not positioned to dedicate themselves entirely to the required military mission. The Committee encouraged the Assistant Secretary of Defense (Health Affairs) to prioritize congressionally directed medical research on substance use disorders aimed at reducing the overall number of opioid-related overdose deaths. The ASADRP has established a network of multidisciplinary, translational research teams with the explicit goal of accelerating the delivery of new or improved treatments for ASUD; as a result, the ASADRP has distributed a total of $40.83M to relevant research.

PROGRAM GOAL

The goal of the program is to support multidisciplinary, team-based translational research efforts to identify promising compounds, proof-of-principle basic research, and human proof-of-concept trials with promising compounds leading to enhanced clinical pharmacological treatment protocols that address effective treatments for ASUD, to include reducing the overall number of opioid-related overdose deaths.

RESEARCH STRATEGY

The overall strategy of the ASADRP supports the following Research Aims:

- ***Aim 1 – Discover:*** Test new chemical entities and repurpose existing medications in preclinical and non-clinical models of ASUD with comorbid PTSD and other psychological disorders.
- ***Aim 2 – Phase 1 First-in-Human Safety:*** Conduct clinical trials of potential medications that include assessment of medical safety and doses for potential efficacy in subjects with ASUD and comorbid PTSD and other psychological disorders.
- ***Aim 3 – Phase 2 Efficacy:*** Conduct multiple site clinical trials to test preliminary efficacy and safety of potential medications or medication combinations in humans with ASUD and comorbid PTSD and other psychological disorders, and to also explore precision medicine tools for matching patients to these medications.

This approach should accelerate the translation of contemporary basic science knowledge into enhanced clinical pharmacological treatment protocols for ASUD, including a regulatory strategy for Food and Drug Administration (FDA) compliance.

"I can't believe I get to be involved in this amazing work to help develop new medications or treatments that could actually significantly improve the lives of Veterans struggling with addiction."

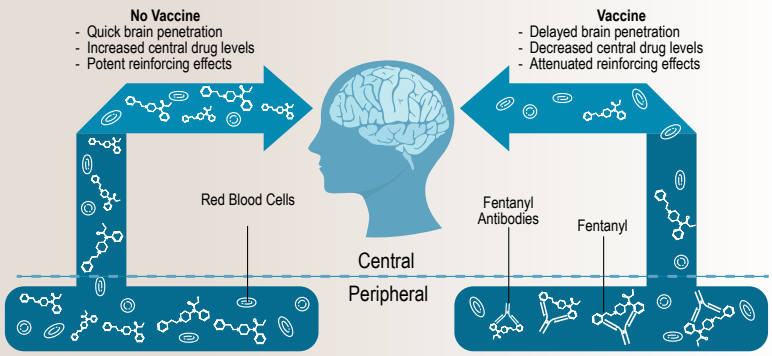
SPC Robert Elder, (U.S. Army, retired), Veterans Engagement Board, FY21 Programmatic Panel Member

[1] Committee on Prevention, Diagnosis, Treatment, and Management of Substance Use Disorders in the U.S. Armed Forces; Board on the Health of Select Populations; Institute of Medicine. 2013. Substance Use Disorders in the U.S. Armed Forces: 2, Understanding Substance Use Disorders in the Military (O'Brien CP, Oster M, and Morden E, Eds.). National Academies Press, Washington, DC. https://www.ncbi.nlm.nih.gov/books/NBK207276/

A translational approach to understanding the complex interaction of ASUD with the military stress comorbidities of PTSD and TBI.

Medication Development of an Anti-Fentanyl Vaccine for Opioid Use Disorder

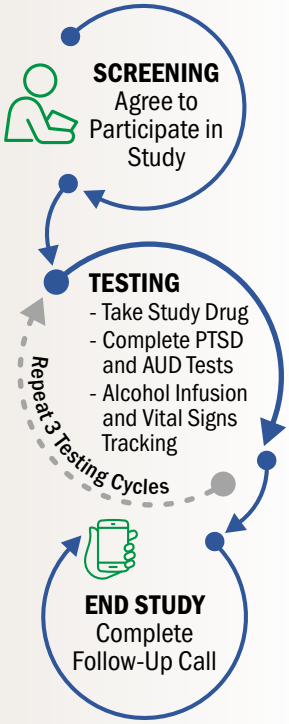
Colin N. Haile, M.D., Ph.D., University of Houston



Opioid use disorder (OUD) or inadvertent exposure to synthetic opioids such as fentanyl (FEN) and its analogs continue to adversely affect Veterans and the general populace, often resulting in death from overdose. This occurs more often in Veterans with PTSD and/or traumatic brain injury (TBI) comorbidities, who appear to be susceptible to developing OUD. Dr. Haile's team has developed an adjuvanted anti-FEN vaccine for OUD and overdose prevention. Study results show that the vaccine completely blocks the analgesic and behavioral effects of high-dose FEN in male and female rats in a manner that is unparalleled. Furthermore, in vaccinated rats compared to non-vaccinated rats, results indicate that the vaccine prevents greater than 90% of high-dose FEN from entering the brain. Based on these data, the University of Houston has initiated the filing of a full patent application and marketing initiative to license the vaccine to interested companies. Newly funded expansion studies will focus on two final experiments in rats: (1) determine whether the vaccine will block FEN-induced drug seeking in an animal model of relapse in humans, and (2) assess the ability of the vaccine to attenuate FEN-induced overdose by monitoring vital physiological measures. The final aim of the expansion studies is to support manufacturing of clinical grade vaccine for toxicology studies with the ultimate goal of conducting phase 1 human clinical trials.

Effect of Sublingual Formulation of Dexmedetomidine HCl (BXCL501) on Ethanol in Heavy Drinkers with PTSD – Alcohol Interaction Study

Ismene Petrakis, M.D., and John Krystal, M.D., Yale University



While there are established pharmacotherapies to treat PTSD and alcohol use disorder (AUD) separately, there are no medications established to treat the patients who have these comorbid disorders. The objective of Dr. Petrakis and Dr. Krystal's study is to determine the safety and efficacy of BXCL501 as a treatment for AUD with comorbid PTSD. This trial is a phase 1, double-blind, placebo-controlled, within-subjects study consisting of three laboratory sessions following pre-treatment with BXCL501 or placebo in a randomized fashion. The team will conduct test sessions to evaluate stress (PTSD) reactivity and alcohol cue reactivity. Study participants will also receive ethanol to assess effects of BXCL501 in combination with ethanol. The team intends to recruit individuals with AUD and PTSD not seeking treatment as well. Eligible participants are to be scheduled for three separate laboratory visits during which they will be randomly assigned to receive sublingual BXCL501 or placebo. Following pre-treatment with BXCL501, participants will undergo the alcohol cue reactivity session, the stress (PTSD) reactivity session, and an ethanol infusion. The team will administer assessments repeatedly throughout the day to measure alcohol craving, PTSD symptoms, cognitive/motor impairment, and physiological changes (e.g., vital signs). Follow-up telephone visits with the participants are planned after each lab day as well as one week after the last lab day. Hopefully, data from this study will support later-phase trials to be conducted, with the end goal of providing those that suffer from AUD and PTSD an effective medication treatment.

AMYOTROPHIC LATERAL SCLEROSIS RESEARCH PROGRAM

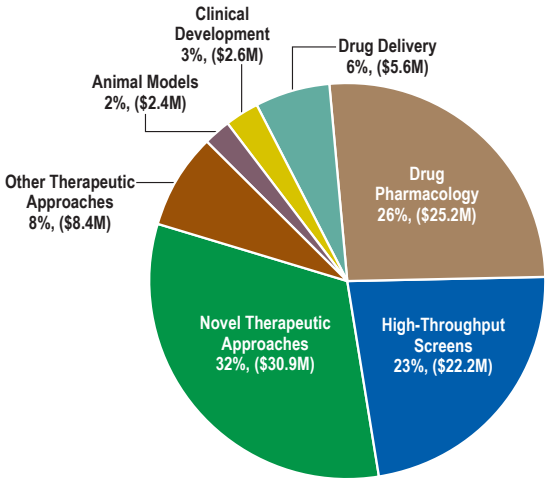
Vision: Improve treatment and find a cure for ALS

Mission: Fund innovative and impactful research to develop new treatments for ALS

PROGRAM HISTORY

In 2007, Congress redirected $5M of Army Research, Development, Test, and Evaluation funding for the Congressionally Directed Medical Research Programs (CDMRP) to initiate the Peer Reviewed Amyotrophic Lateral Sclerosis Research Program (ALSRP) as a broadly competed, peer-reviewed research program. The overall goal of the program has been to expedite the pathway from bench science to clinical trials for new therapeutic approaches in amyotrophic lateral sclerosis (ALS). With a total appropriation of more than $140M, over 100 projects have been funded, many of which are still in progress. From these funded efforts, four promising new ALS drug candidates have moved into advanced drug development, and three have advanced to early-phase clinical trials.

Through FY19, the portfolio was narrowly focused on therapeutic discovery and preclinical validation research projects, with the intent to identify new ALS drug candidates and move them into advanced drug development. Recent increases in the ALSRP congressional appropriation, from $10M to $20M in FY20, enabled the program to increase investments in innovative therapeutic development and also expand into clinical therapeutic approaches. In FY20, the ALSRP offered a mechanism focused on leveraging human-based ALS resources and repositories to enrich clinical trials or optimize components of current clinical care.



FY07-FY20 ALSRP Portfolio Investment

MILITARY RELEVANCE

ALS impacts U.S. Service Members and Veterans: Research supports the idea that people who have served in the military are at a greater risk of developing ALS than those with no history of military Service. In 2006, the National Academy of Medicine conducted a review and concluded that there was sufficient evidence to support an association between military deployment and risk of developing ALS. Subsequently, the U.S. Department of Veterans Affairs (VA) implemented regulations to establish a presumption of Service connection for ALS. Importantly, the regulation acknowledges the link between military Service and increased risk for ALS. Resources are needed to care for Service Members, Veterans, and their family members living with ALS today. The benefits of the treatment-focused research by the ALSRP extend to Service Members, Veterans, and their family members living with ALS today.

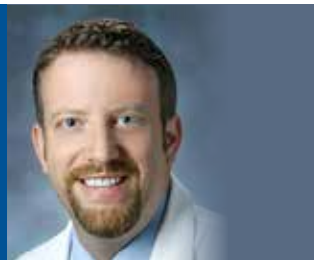
2020 Congressional Appropriations, Research Investment, and Withholds and Management Costs

Congressional Appropriations	Research Investment	Withholds and Management Costs
$20M	Clinical Development Award (New in FY20)..... $2,357,149 Therapeutic Development Award..... $2,619,986 Therapeutic Idea Award ..... $12,174,837 Modifications to ongoing awards..... $985,750	USAMRDC[1] ..... $378,397 SBIR/STTR[2] ..... $671,000 Mgt Costs (4.29%) $812,881
Total: $20M	**Total:** $18,137,722	**Total:** $1,862,278

[1] USAMRDC - U.S. Army Medical Research and Development Command; [2] SBIR/STTR - Small Business Innovation Research/Small Business Technology Transfer

"ALS patients, caregivers, and advocates are involved in all aspects of ALSRP peer review, program policy, investment strategy, and research focus discussions. Based on important stakeholder input, in FY20 we prioritized funding of novel innovative ideas through the Therapeutic Idea Award, provided greater emphasis on biomarker development to improve and de-risk eventual clinical trials, added the new Clinical Development Award, and emphasized open data and resource sharing."

Lyle Ostrow, M.D., Ph.D., Johns Hopkins School of Medicine, FY20-FY21 Programmatic Panel Chair



CLINICAL DEVELOPMENT ON THE HORIZON

New Clinical Development Award Mechanism – FY20 Awards

In FY20, the ALSRP offered the Clinical Development Award (CDA) for the first time. The CDA supports correlative studies leveraging human-based ALS resources to enrich clinical trials or optimize components of current ALS clinical care. Leveraging can refer to use of existing well-characterized and highly curated resources or collaboration with ongoing clinical research to amplify potential gains in knowledge. In FY20, the ALSRP funded six CDAs, which are briefly described in the following table.

Institution Principal Investigator (PI)	Project Description
Annexon, Inc. Enchi Liu	Multi-center, open-label, proof-of-biology study of intravenous ANX005. Assessing the safety, tolerability, and pharmacokinetics of ANX005 administered in patients with ALS.
Columbia University Medical Center Wassim Elyaman	Examining the fused in sarcoma-antisense-oligonucleotide (FUS-ASO) clinical trial to perform longitudinal deep dissection of the immune response in symptomatic and asymptomatic ALS individuals with mutated FUS to identify novel molecular targets that can be engaged for ALS therapy.
Pennsylvania State University, Milton S. Hershey Medical Center Andrew Geronimo	A longitudinal home study of ALS patients to assess bulbar progression via a smartphone-based, self-administered remote speech and swallow assessment.
Massachusetts Institute of Technology Ernest Fraenkel	Identifing biological pathways that define subtypes of ALS by leveraging the AnswerALS biorepository.
Emory University Christina Fournier	Building an ALS outcome measure toolbox containing a widely accessible patient-reported questionnaire to assess overall disability and a novel objective exam-based scale to assess overall motor strength using Rasch methodology.
ALS Therapy Development Institute Fernando Vieira	Using the SomaScan proteomics platform to assess 5,000 potential proteins in blood samples to discover prognostic biomarkers of ALS disease progression.

Program Priorities	Preclinical Treatment Discovery	Preclinical Treatment Validation	Clinical Research
	• Animal and cell models • High-throughput screens • Identify candidate drug leads • Measure drug-target engagement	• Secondary validation and drug delivery • Optimization of drug properties • Collect data for FDA submission • Develop Good Manufacturing Practices methods	• Encourage use of established ALS patient repositories • Promote correlation of patient samples with clinical outcomes • Optimize current ALS clinical care strategies
Funding Mechanisms	**Therapeutic Idea Award**	**Therapeutic Development Award**	**Clinical Development Award**
	• FY10–present • Identify candidate drugs in high-throughput screens • Validate resulting drug candidates, assess pharmacological properties, and demonstrate effect on intended molecular targets	• FY07–present • Ready candidate drugs for clinical trials by secondary validation, optimization of pharmacological properties, development of manufacturing processes, and compilation of data for FDA submissions • Develop markers to demonstrate drug actions on intended molecular targets	• New for FY20! • Leverage human subject-based resources through correlative clinical research to better define subtypes, predict therapeutic response, assess prognosis, and optimize components of current ALS clinical care • Correlate clinical trial-related biosamples, imaging, or epidemiological data with clinical outcomes

AUTISM RESEARCH PROGRAM

Vision: Improve the lives of individuals with autism spectrum disorders now

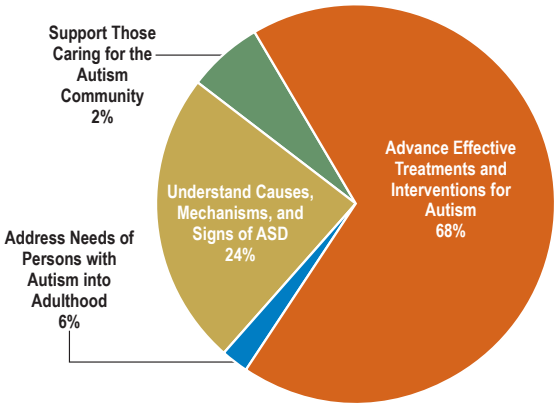
Mission: Promote innovative research that advances the understanding of autism spectrum disorders and leads to improved outcomes for Service Members, their families, and the American public

PROGRAM HISTORY

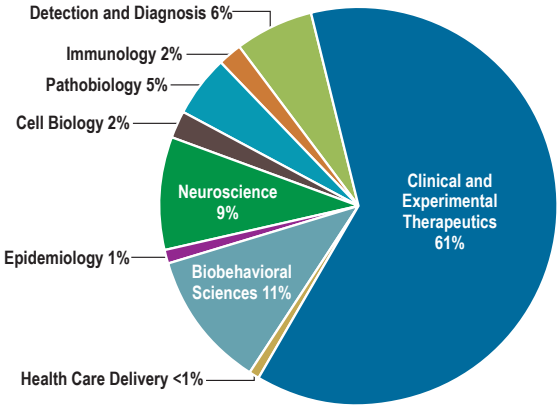
Since its inception in FY07, through FY20, appropriations totaling $104.4M have been directed to the Peer Reviewed Autism Research Program (ARP) to promote innovative research that advances the understanding of autism spectrum disorder (ASD). The immediacy of ARP's vision, to improve the lives of individuals with ASD now, has imparted a strong sense of action and continues to steer the investment strategy for ARP. ARP focuses on funding innovative and highly impactful research while trying to complement other funding agencies' initiatives.

The causes of ASD are unknown; however, progress is being made on several fronts, and the answers will likely be multifaceted. ASD encompasses a wide range of complex developmental disorders, with characteristics from mild to severe in social, emotional, and communication abilities. Additionally, many individuals living with ASD are afflicted with co-occurring conditions (e.g., anxiety, gastrointestinal [GI] issues, sleep disorders, and aggression) that are not well understood. The population of ASD individuals entering adulthood is growing, and ARP recognizes the critical need for supporting and treating adults with ASD.

The ARP Areas of Interest are topics identified for increased emphasis and need in the scientific setting or the consumers' daily lives. Through the program's Areas of Interest, the ARP places emphasis on research that assists ASD individuals in their transition to adulthood, as well as research aimed at improving healthcare delivery to adults with ASD. The ARP also focuses on ways to improve diagnosis, treatment, and co-occurring conditions to enable a better life for those with autism and their families. Recent progress by investigators funded by ARP shows promise in the areas of (1) alleviating the core symptoms of ASD; (2) understanding and treating the conditions that co-occur with ASD, with a focus on GI issues, sleep, and anxiety; (3) understanding the needs of adult individuals with ASD; and (4) supporting those caring for the autism community.



FY16-FY20 ARP Portfolio Investment by Strategic Goal



FY16-FY20 ARP Portfolio Investment by Scientific Classification System (SCS) Code

2020 Congressional Appropriations, Research Investment, and Withholds and Management Costs

Congressional Appropriations	Research Investment	Withholds and Management Costs
$15M	Clinical Translational Award ..... $2,649,505 Clinical Trial Award ..... $6,533,138 Idea Development Award ..... $4,220,418 Modifications to ongoing awards $85,000	USAMRDC ..... $66,940 SBIR/STTR ..... $503,000 Mgt Costs (6.53%) $941,999
Total: $15M	**Total:** $13,488,061	**Total:** $1,511,939

"My experience as an Autism Research Program reviewer was so exciting. I was amazed at how much of the research I understood and how so many people were trying to help the autistic community! I cannot stress enough how important research is when it comes to moving forward with finding new therapies and treatments that can help the autistic community. Without solid research, a lot of families would not be where we are at today with our loved ones and helping them move forward in their lives."

Jennifer Bittner, Autism Speaks, FY20-FY21 Consumer Peer Reviewer

ARP-FUNDED HIGHLIGHTS BY STRATEGIC GOAL

The ARP has identified four near- to mid-term goals to achieve in the next 5 to 7 years to continue to accelerate research in the autism community. These strategic goals include (1) Understand causes, mechanisms, and signs of ASD; (2) Advance effective treatments and interventions for autism; (3) Address needs of persons with autism into adulthood; and (4) Support those caring for the autism community.

Understand Causes, Mechanisms, & Signs of ASD

AR150143: Prenatal Polyunsaturated Fatty Acid Levels and Risk of Autism Spectrum Disorders
PI: Kristen Lyall, Sc.D.

Dr. Lyall's research team is examining the relationship between polyunsaturated fatty acids (PUFA) levels and ASD to determine whether levels of PUFAs measured from maternal blood samples and newborn blood spots differ between children with and without ASD. In addition, the research team aims to explore how the relationship between PUFAs and ASD differs among race/ethnicity, preterm birth, and child gender. Results from this study suggest an increased risk for having a child with ASD with comorbid intellectual disability among mothers with low levels of certain PUFAs. These findings provide novel information and suggest the need to further examine the association between PUFAs and neurodevelopmental outcomes.

Address Needs of Persons with Autism into Adulthood

AR170121: Surviving and Thriving in the Real World: A Daily Living Skills Intervention for High Schoolers with Autism Spectrum Disorder
PI: Amie Duncan, Ph.D.

Dr. Duncan's team aims to continue refining the Surviving and Thriving in the Real World (STRW) intervention, a group treatment for high school adolescents with ASD and their parents that targets specific daily living skills (DLS) (i.e., hygiene, grocery shopping, managing money) by conducting a pilot randomized clinical trial to examine how participation in STRW affects outcomes. To date, there are no interventions that target the acquisition of DLS. STRW is an evidenced-based strategy to teach DLS, with the potential to directly affect current functioning and future adult outcomes by increasing capabilities for skills that are needed to succeed in employment, college, and independent living.

Advance Effective Treatments & Interventions for Autism

AR160059: A Multidisciplinary Intervention for Encopresis in Children with ASD
PI: Nathan Call, Ph.D., BCBA-D

In response to the absence of treatment for incontinence among individuals with ASD, Dr. Call's research team aims to design a 2-week multidisciplinary intervention for encopresis (MIE) that combines medical and behavioral approaches. The overall goal of this study is to demonstrate the efficacy of MIE and identify moderators that predict success of MIE in a randomized controlled trial of 150 children with ASD. This study is the first large-scale clinical trial of a treatment for MEI in individuals with ASD and will set the foundation for future research and clinical guidelines.

Support Those Caring for the Autism Community

AR180072: A Novel Provider-Focused Training Program to Serve Transition-Age Youth and Adults with Autism Spectrum Disorder
PI: Dr. Beth Malow, M.D.

In response to the shortage of healthcare providers with knowledge and expertise in ASD, Dr. Malow and her team plan to develop and test a novel primary care provider (PCP) training program, with the goal of increasing high-quality community-based healthcare for adults with ASD. The Project Extension for Community Healthcare Outcomes (Project ECHO) uses a secure videoconferencing technology to create a learning community by connecting PCPs in local communities to a team of experts. Since the start of this project, Dr. Marlow's team has collected data from adults with ASD, caregivers, and PCPs to inform the development of an ECHO Autism Transition/Adult Healthcare program and to reveal primary themes and subthemes pertaining to both positive and negative healthcare experiences and suggestions for improvement. Future activities for this study include the implementation and testing of the first ECHO training program.

BONE MARROW FAILURE RESEARCH PROGRAM

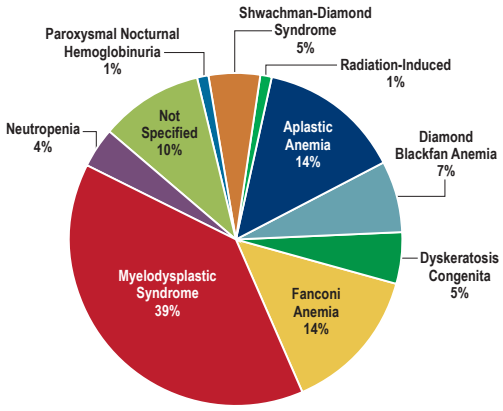
Vision: To understand and cure bone marrow failure diseases

Mission: To encourage and support innovative research that is committed to advancing the understanding and treatment of inherited and acquired bone marrow failure diseases, thereby improving the health of affected Service Members, Veterans, and the general public, with the ultimate goals of prevention and cure

PROGRAM HISTORY

Congress initiated the Peer Reviewed Bone Marrow Failure Research Program (BMFRP) in FY08 to provide support for exceptional innovative research focused on bone marrow failure (BMF) diseases. From FY08 through FY20, $41.55M has been appropriated by Congress to research the prevention, causes, and treatment of BMF diseases. Thus far, the BMFRP has funded 82 awards, with the mission to support innovative research committed to advancing the understanding of inherited and acquired BMF diseases. The appropriation for FY21 for the BMFRP is $7.50M.

The cavities of bones are made up of a spongy tissue that contains stem cells capable of maturing to blood cells in a process known as hematopoiesis. The hematopoietic cascade is responsible for the development of all cellular blood components, including red blood cells, white blood cells, and platelets. Disorders affecting the stem cells or progenitor cells can lead to BMF – rare, potentially life-threatening diseases in which the bone marrow stops functioning or produces abnormal blood cells. These diseases can be either inherited or acquired. Inherited BMF includes a group of diseases in which somatic genetic mutations lead to a deficiency in hematopoiesis that presents itself in childhood or early adulthood. Acquired BMF includes a group of diseases that can occur following an environmental exposure such as ionizing radiation, chemical contamination, or the long-term effects of chemotherapeutics. Both types of BMF lead to life-long chronic illnesses with the potential to develop cancer.



FY08-FY20 BMFRP Portfolio Investment by Disease Classification

"Bone marrow failure disorders are often categorized as 'rare diseases' and the experiences of people living with them easily show how powerful an impact 'rare' can have. That rarity is one of the single greatest factors influencing any of our lives. And while these diseases can easily drag people into a numb and jaded existence, waiting for the next shoe to drop, discoveries from research buoy many of us and give hope in the promise of a better tomorrow. Research has given many of us lifelines we could never have imagined. Research allows us to be more than patients and statistics; it allows us to shed those labels and be people."

Duncan E. Nunes, Fanconi Anemia Research Fund, FY20-FY21 Consumer Peer Reviewer

2020 Congressional Appropriations, Research Investment, and Withholds and Management Costs

Congressional Appropriations	Research Investment	Withholds and Management Costs
$3.0M	Idea Development Award $2,527,789	USAMRDC ..... $57,810 SBIR/STTR ..... $109,500 Mgt Costs (10%) $304,901
Total: $3.0M	**Total:** $2,527,789	**Total:** $472,211

"I am honored to serve as a member of the BMFRP. The researchers, reviewers, and consumer advocates who participate are profoundly dedicated to advancing the mission of the research program and to the patients. For many BMF syndromes, we still lack fundamental knowledge on their cause. Due to this gap in knowledge, these rare and devastating disease have few, if any, treatment options. The BMFRP is incredibly important to providing critical funding to advance our knowledge of these diseases and provide new treatments for the patients."
Dan Starczynowski, Ph.D., University of Cincinnati, FY19-FY21 Programmatic Panel Chair

THERAPIES IN THE PIPELINE

Functional Rescue of Definitive Hematopoietic Potential in Stem Cells Harboring Telomerase Mutations Associated with BMF

Luis Batista, Ph.D., Washington University

Aplastic anemia (AA) and dyskeratosis congenita are two BMF conditions that often possess mutations in the cellular machinery responsible for telomere maintenance and display impeded hematopoietic output. Through an FY16 Idea Development Award (IDA) – Early Career Investigator, Dr. Luis Batista and his team identified a novel molecular pathway that can reinstate hematopoietic output in cells with these mutations. The team also discovered pathways that can greatly enhance the production capacity of functional hematopoietic cell lines in vitro. Inhibition of noncanonical poly(A) polymerase PAP-associated domain-containing 5 (PAPD5), a polymerase that impairs the telomerase RNA component (TERC), resulted in lengthened telomeres and restored regular telomerase activity. PAPD5 regulation may also represent a novel therapeutic avenue to manage the diseases.

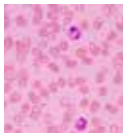
Novel Therapeutics for BMF Disorders Due to Telomere Exhaustion

Suneet Agarwal, M.D., Ph.D., Boston Children's Hospital

With an FY18 IDA – Established Investigator, Dr. Suneet Agarwal and his team expanded the knowledge base of the molecular mechanisms surrounding BMF syndromes that occur as a result of impaired telomere maintenance. Telomeres are non-coding repeat sections located on the end of chromosomes that serve a protective role and are maintained by the enzyme telomerase. Using stem cells from patients with BMF-triggering genetic mutations, Dr. Agarwal's team identified a class of drugs that reversed the telomerase insufficiency characteristically found in these patients. These findings exemplify a promising treatment for BMF conditions caused by impaired telomere maintenance, ready for the next stage of translation.

The Role of Nemo-Like Kinase in the Pathogenesis and Treatment of DBA

Kathleen Sakamoto, M.D., Ph.D., Stanford University



Diamond Blackfan anemia (DBA) is a genetic BMF disorder that is typically associated with hypoplastic anemia, congenital abnormalities, and an increased disposition to developing cancer. A quarter of DBA patients have mutations in the ribosomal protein S19 (RPS19) gene and a resultant hyperactivation of nemo-like kinase (NLK) only in the erythroid progenitors. With an FY18 IDA – Established Investigator, Dr. Kathleen Sakamoto's team is investigating the ability of SD208, metformin, and other small molecules to decrease NLK activity and expression, respectively. Early findings demonstrate that both drugs improve erythropoiesis (the production of mature red blood cells) in culture assays. The team is in the process of characterizing signaling pathway activity downstream of NLK following inhibition in human RPS-insufficient erythroid progenitor cells. A provisional patent for this study has been obtained by the research team.

Ex Vivo-Generated Autologous iTregs as a Cell-Based Therapy for Acquired AA

Lisa Minter, Ph.D., University of Massachusetts Amherst

T effector cells and naturally occurring regulatory T cells (nTregs) are frequently dysfunctional and show aberrant activation in patients with acquired AA. nTregs immunosuppressive therapies have recorded some success, but the lengthy preparation process and other limitations have reduced the overall practicality of this treatment technique. Through funding from an FY18 IDA – Established Investigator, Dr. Lisa Minter investigated a new method that generates induced regulatory T cells (iTregs) using synthetic cell-penetrating peptide mimics. Employing a humanized mouse model, the research team demonstrated efficacy of the iTregs in lessening the disease severity and improving survival when administered during BMF induction. Analysis continues to further define the mechanistic process of iTregs induction and to further develop this treatment of immune-mediated BMF disease.

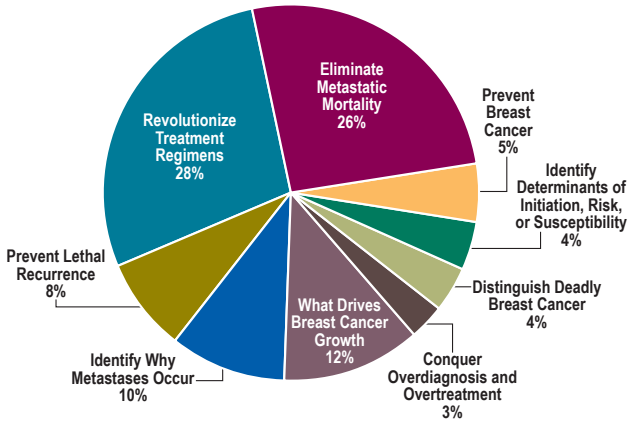
BREAST CANCER RESEARCH PROGRAM

Vision: A world without breast cancer

Mission: To end breast cancer for Service Members, Veterans, and the general public by funding innovative, high-impact research through a partnership of scientists and consumers

PROGRAM HISTORY

The Peer Reviewed Breast Cancer Research Program (BCRP), established in 1992 as a result of breast cancer advocacy and congressional support, has received more than $3.9B in congressional appropriations through FY21. BCRP-supported research has led to the development of new standard-of-care treatments, diagnostic and imaging approaches, risk assessment tests, and resources for the breast cancer research and patient communities. For example, preclinical research supported by the BCRP contributed to four FDA-approved drugs: trastuzumab, palbociclib, ribociclib, and abemaciclib.



FY13-FY20 BCRP Portfolio Investment by Overarching Challenge

BREAST CANCER RELEVANCE TO MILITARY HEALTH

Breast cancer causes the most cancer-related deaths in women under the age of 40.[1] Female active-duty Service Members have a 20%-40% higher incidence rate than the general public.[2] The incident rate for active-duty women is seven times higher than the average incident rate of 15 other cancer types across all Service Members.[3]

OVERARCHING CHALLENGES

The BCRP recognizes that many overarching questions remain unanswered in breast cancer, and funding must be invested in critical areas of research to make breakthroughs that will save lives and lead to eradication of this disease. To meet this urgent need, the BCRP requires all applications to address at least one of the following overarching challenges within the Breast Cancer Landscape:[4]

- Prevent breast cancer (primary prevention)
- Identify determinants of breast cancer initiation, risk, or susceptibility
- Distinguish deadly from non-deadly breast cancer
- Conquer the problems of overdiagnosis and overtreatment
- Identify what drives breast cancer growth; determine how to stop it
- Identify why some breast cancers become metastatic
- Determine why/how breast cancer cells lie dormant for years and then re-emerge; determine how to prevent lethal recurrence
- Revolutionize treatment regimens by replacing them with ones that are more effective, less toxic, and impact survival
- Eliminate the mortality associated with metastatic breast cancer

2020 Congressional Appropriations, Research Investment, and Withholds and Management Costs

Congressional Appropriations	Research Investment		Withholds and Management Costs	
$150M for Breast Cancer Research **$454,128** proceeds from the Stamp Out Breast Cancer Act	Breakthrough Award – Funding Level 1	$20,770,759	USAMRDC	$2,899,349
	Breakthrough Award – Funding Level 2	$58,638,530	SBIR/STTR	$5,031,000
	Breakthrough Award – Funding Level 3	$7,816,999	Mgt Costs (5.72%)	$8,132,517
	Era of Hope Scholar Award	$9,227,979		
	Expansion Award	$3,992,748		
	Transformative Breast Cancer Consortium Award	$30,959,678		
	Modifications to ongoing awards	$2,984,570		
Total: $150,452,128		**Total:** $134,391,263		**Total:** $16,062,866

[1] www.cdc.gov/cancer/dataviz

[2] Zhu K, Devesa SS, Wu H, et al. 2009. Cancer incidence in the U.S. military population: Comparison with rates from the SEER program. *Cancer Epidemiol Biomarkers Prev* 18(6): 1740-1745.

[3] Lee T, Williams VF, Taubman, SB, and Clark, LL. 2016. Incident diagnoses of cancers in the active component and cancer-related deaths in the active and reserve components, U.S. Armed Forces, 2005–2014. *Medical Surveillance Monthly Report* 23(7): 23-31.

[4] https://cdmrp.army.mil/bcrp/pdfs/Breast%20Cancer%20Landscape2020.pdf

"My husband and I were raised within the DOD. We feel a deep and continuing obligation to support our military, and my serving as a DOD BCRP consumer reviewer is one small way for me to give back. Based on the breast cancer researchers I have met over the years, their commitment to ultimately ending breast cancer is total. It is a joy to meet new scientists who have worked in labs but never met a breast cancer survivor. Without exception they express a renewed commitment to their work on our behalf."

Carol McWilliams, Inflammatory Breast Cancer Research Foundation, FY17-FY20 Consumer Peer Reviewer

RESEARCH ADVANCES IN TREATMENT REGIMENS

De-Escalating Treatment in HER2+ Breast Cancer Based on Predictive Biomarkers

Mothaffar F. Rimawi, M.D., and Rachel Schiff, Ph.D., Baylor College of Medicine

Genetic amplification or overexpression of the human epidermal growth factor receptor 2 (HER2) oncogene drives HER2+ breast cancer. For ~25% of patients with HER2+ breast cancer, dual HER2-blockade, such as trastuzumab + lapatinib, without chemotherapy results in pathologic complete response. The remaining 75% of patients have improved clinical outcomes with HER-2 targeted treatments plus additional chemotherapy. Drs. Rimawi and Schiff evaluated HER2-overexpressing patient breast tumors for biomarkers that correlated with clinical response after trastuzumab + lapatinib therapy. Findings from this important work suggest that baseline phosphinositol-3-kinase pathway activity and/or HER2 mRNA levels could help identify patients responsive to anti-HER2 therapy alone, allowing for a de-escalation of patient exposure to chemotherapy.

Publications:

Veeraraghavan J, De Angelis C, Mao R, et al. 2019. A combinatorial biomarker predicts pathologic complete response to neoadjuvant lapatinib and trastuzumab without chemotherapy in patients with HER2+ breast cancer. *Ann. Oncol.* 30(6):927-933.

Prat A, Pascual T, De Angelis C, et al. 2020. HER2-enriched subtype and ERBB2 expression in HER2-positive breast cancer treated with dual HER2 blockade. *J. Natl. Cancer Inst.* 112(1):36-44.

Fasting-Mimicking Diet and Hormone Therapy Induce Regression of Breast Cancer

Valter Longo, Ph.D., University of Southern California, and Alessio Nencioni, Ph.D., University of Genoa

Resistance to anti-estrogen therapies (e.g., fulvestrant) remains a problem for patients with hormone receptor positive (HR+) breast cancer. Fasting or Fasting-Mimicking Diets (FMDs) reduce the level of growth factors that enhance tumor cell estrogen receptor activity, suggesting these dietary interventions could delay resistance. Drs. Longo and Nencioni showed that in a HR+ mouse model, combining FMD with fulvestrant and palbociclib (a cyclin-dependent kinase 4/6 inhibitor) prevented tumor growth and led to tumor shrinkage. In addition, mouse tumors resistant to fulvestrant + palbociclib treatment could be re-sensitized after cycles of FMD. Importantly, in clinical trials of HR+ breast cancer patients receiving anti-estrogen therapy, periodic FMD led to metabolic changes analogous to the mouse model findings. These results provide rationale for larger clinical trials of FMD as an adjuvant to anti-estrogen therapy to improve clinical outcomes in patients with HR+ breast cancer.

Publication:

Caffa I, Spagnolo V, Vernieri C, et al. 2020. Fasting-mimicking diet and hormone therapy induce breast cancer regression. *Nature* 583(7817):620-624.

BCRP-FUNDED CLINICAL TRIALS FOCUSED ON PREVENTION

Denosumab (XGEVA®); Phase 3

Judy Garber, M.D., M.P.H., Dana-Farber Cancer Institute, Christian Singer, M.D., M.P.H., Austrian Breast & Colorectal Cancer Study Group

This phase 3 clinical trial (BRCA-P) will determine whether inhibition of receptor activator of nuclear factor kappa-B ligand (RANKL) with denosumab can prevent breast cancer in women who carry a germline BRCA1 mutation. In addition, the study will assess quality of life, changes in breast density, impacts on tumor phenotype and molecular profile, and whether serum osteoprotegrin levels are associated with breast cancer risk. The BRCA-P trial, co-funded between the BCRP and the National Cancer Institute (NCI) Alliance for Clinical Trials in Oncology NCI Community Oncology Research Program, will recruit subjects from Australia, Austria, Germany, Israel, Spain, the United Kingdom, and the United States. As of 2021, numerous BCRP-funded sites are open for recruitment. (EudraCT Number: 2017-002505-35).

Alpha-Lactalbumin Vaccine; Phase 1

Vincent Tuohy, Ph.D., and Thomas Budd, M.D., Cleveland Clinic Foundation

This phase 1a clinical trial will evaluate the dosage and safety for alpha-lactalbumin vaccination in individuals who have recently been diagnosed with triple-negative breast cancer and have recovered from current standard of care. After completion of the phase 1a trial, a phase 1b trial will be conducted to evaluate the safety of alpha-lactalbumin vaccination in healthy, cancer-free individuals who have voluntarily elected to undergo mastectomy as prophylaxis due to high genetic and/or familial risk for breast cancer. An Investigational New Drug (IND) application for the phase 1a trial is in place as of December 2020, and the trial opened for accrual in October 2021. (NCT04674306)

CHRONIC PAIN MANAGEMENT RESEARCH PROGRAM

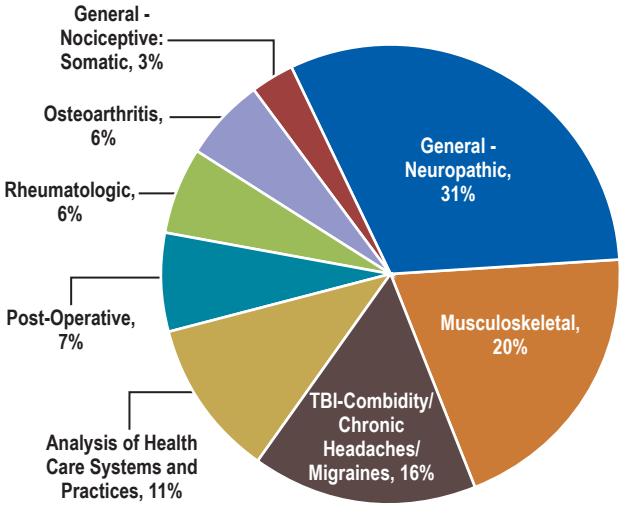
Vision: Improving the medical readiness of Service Members, as well as the quality of life and level of function of all Americans, with or at risk for developing chronic pain

Mission: To support and promote innovative, high-impact research to prevent the development and improve the management of chronic pain

PROGRAM HISTORY

In FY19, a congressional appropriation of $10M established the Chronic Pain Management Research Program (CPMRP). Prior to this, chronic pain research had been supported by Broad Agency Announcements and other CDMRP programs. From FY06 through FY18, the CDMRP has overseen an investment of over $174M in chronic pain research. The CDMRP also participates in the Pain Management Collaboratory, an interagency effort with the National Institutes of the Health (NIH) and VA supporting pragmatic clinical trials for non-pharmacological approaches to pain management.

Through FY20, the CPMRP managed $25M in congressional appropriations. The program strongly encourages stakeholder engagement and partnerships with relevant military and Veteran medical professionals and facilities. Of the FY19-FY20 funds, 20% supported research at a DOD or VA institution. Through FY20, the CPMRP received a total of 135 compliant applications: 24 for Translational Research Awards and 111 for Investigator-Initiated Research Awards. Following recommendations from the CPMRP Programmatic Panel members, the CPMRP funded 3 Translational Research Awards and 14 Investigator-Initiated Research Awards. The CPMRP is committed to supporting research endeavors with the potential of producing the next generation of preventative and pain management treatments to improve the health and well-being of our Service Members, Veterans, and the American public.



FY19–FY20 CPMRP Portfolio Investment by Research Focus or Pain Type

"Improving pain management in the wounded Service Member is perhaps one of the finest uses of a physician researcher's time."

COL Chester "Trip" Buckenmaier III (U.S. Army, retired), M.D., Program Director, Defense and Veterans Center for Integrative Pain Management, Professor, Anesthesiology, Uniformed Services University of the Health Sciences, FY20 Programmatic Panel Member

2020 Congressional Appropriations, Research Investment, and Withholds and Management Costs

Congressional Appropriations	Research Investment	Withholds and Management Costs
$15M	Investigator-Initiated Research Award .....$10,236,814 Translational Research Award $3,421,687	USAMRDC .....$289,940 SBIR/STTR .....$503,000 Mgt Costs (3.86%)....$548,559
Total: $15M	**Total:** $13,658,501	**Total:** $1,341,499

FY20 CPMRP AWARDS BY RESEARCH FOCUS OR PAIN TYPE

General – Neuropathic

Investigating Mechanisms and Therapies for Chronic Neuropathic Pain: The Role of TNFR2

John Bethea, Ph.D., Drexel University

Development of a Small Chemical Drug That Targets EphB1 for the Treatment of Chronic Pain

Mark Henkemeyer, Ph.D., University of Texas Southwestern Medical Center at Dallas

Analysis of Health Care Systems and Practices

Machine Learning for Chronic Pain Management Optimization Within a Health Equity Framework

Krista Highland, Ph.D., Uniformed Services University of the Health Sciences

The Relationship Between Type of Opioid Used During Critical Illness and Transition to Chronic Pain

Hannah Wunsch, M.D., Sunnybrook Research Institute

Musculoskeletal

Acute to Chronic Pain Signatures in Traumatic Injury

Jennifer Nyland, Ph.D., Pennsylvania State University, Milton S. Hershey Medical Center

Post-Operative

Development and Validation of Predictive Models for Transition from Acute to Persistent Pain After Major Surgery

Simon Haroutunian, Ph.D., Washington University

Rheumatologic

Pain and the Immune System: A Novel Therapeutic Approach

Richard Traub, Ph.D., University of Maryland, Baltimore

General – Nociceptive: Somatic

Non-Opioid Chronic Pain Treatment by Erasing Spinal Pain Memory

Jun-Ho La, D.V.M., Ph.D., University of Texas Medical Branch at Galveston

TBI-Comorbidity/Chronic Headache/Migraine

Prevention of Pain Chronification and Neuroinflammation After Traumatic Brain Injury by Neuroprotectin D1 and GPR37 Signaling

Ru-Rong Ji, Ph.D., Duke University

Combined Non-Pharmacological Therapies for MTBI-Related Headaches

Albert Leung, M.D., Veterans Medical Research Foundation of San Diego

COMBAT READINESS – MEDICAL RESEARCH PROGRAM

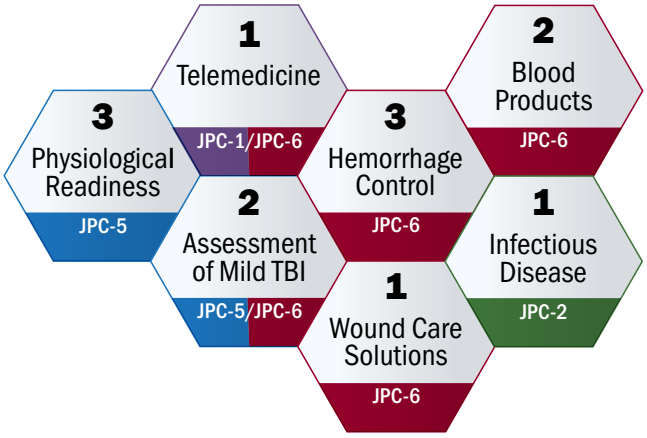
Vision: Deliver high-impact medical solutions in diverse operational settings and closer to the point of injury to increase survivability and readiness of the Warfighter

Mission: Develop innovative solutions to increase medical readiness, mitigate fatalities, optimally treat life-threatening injuries, and promote positive long-term outcomes

PROGRAM HISTORY

Congress established the Combat Readiness – Medical Research Program (CRRP) in FY19 to pursue military-relevant advanced technology and therapeutic research related to forward-deployable solutions that can promptly address life-threatening injuries, medical threats, and treatments for Service Members in battlefield settings. From FY19 through FY21, the CRRP received $35M in congressional appropriations. The congressional language for the CRRP encompasses research that would enable the Warfighter to better respond to serious injury and mitigate the long-term effects of battlefield trauma in rural and austere environments, as well as solutions that can translate to prolonged prehospital civilian trauma care in situations of mass casualty events and/or extended disrupted communications in dense urban or subterranean environments. Synergistic topics related to medical combat readiness research have been supported by the Defense Health Program Core and other Congressional Special Interest programs that are managed by the CDMRP. The research funded by the CRRP aligns to high-priority military capability gaps, which are coordinated through the planning and execution activities of the Joint Program Committees (JPCs) and the U.S. Army Medical Materiel Development Activity (USAMMDA). In FY21, the CRRP released its Strategic Plan, which outlines the near-term and long-term priorities of the program, including these synergistic efforts to fund rapidly translatable technology for the Warfighter to enhance combat readiness.

Alignment of FY19-FY20 CRRP Projects Funded to Military Capability Gaps



USAMMDA and Advanced Development: JPC-1 Medical Simulation and Information Sciences; JPC-2 Military Infections Diseases Research Program; JPC-5 Military Operational Medicine Research Program; JPC-6 Combat Casualty Care Research Program

"The CRRP works to address the unmet needs of medical combat readiness and extend state-of-the-art trauma care into the current and future battlespace of austere, remote, and prolonged care settings. The Programmatic Panel represents leaders of the full enterprise of the military's combat casualty care programs, aimed at delivering clinical breakthroughs and transformational, Warfighter-centric solutions to the field through military, academic, and industry collaborations. As the CRRP Chair, we intend to maximize every investment to improve the care of our Service Members in diverse operational settings."

Vikhyat Bebarta, M.D., University of Colorado, Denver, FY19-FY21 Programmatic Panel Chair

2020 Congressional Appropriations, Research Investment, and Withholds and Management Costs

Congressional Appropriations	Research Investment	Withholds and Management Costs
$10M	Rapid Development and Translational Research Award .....$8,919,623 Modifications to ongoing awards.....$257,009	USAMRDC .....$185,333 SBIR/STTR .....$335,000 Mgt Costs (3.2%) $303,035
Total: $10M	**Total:** $9,176,632	**Total:** $823,368

"Being able to influence and shape the latest and greatest in medical technology for the Warfighter, Veterans, and the American people is a huge honor. Being on the ground level of some of this revolutionary technology and its funding sources make hard lessons learned on the battlefield easier to tolerate. The value that the other panel members and the CDMRP as a whole place on the words of the consumer reviewers is very humbling and emphasizes the true importance of this work."

Samuel Patrick (Washington Army National Guard), FY19-FY20 Consumer Peer Reviewer

FY21 FOCUS AREAS:

- Solutions to enhance Warfighter readiness, such as solutions to address:
  - Infectious diseases
  - Sleep disorders
  - Myalgic encephalomyelitis/chronic fatigue syndrome
  - Service-related post-traumatic arthritis
- Solutions to enhance combat care delivery throughout the far-forward environment, such as:
  - Telemedicine solutions that enable medical capabilities at far-forward battlespace locations worldwide
  - Medical simulation technology that supports sustainment of critical skills and medical decision-making
  - Freeze-dried plasma and platelets
  - Ruggedized oxygen generation systems
  - Solutions for the assessment of mild traumatic brain (mTBI) injury, to include portable devices
- Wound-care solutions for complex trauma and tissue regeneration that span the operational medical care continuum or roles of care (e.g., acute through chronic care), such as:
  - Multi-modal wound-care solutions that provide a combination of hemostasis, wound healing, infection prevention, and/or analgesia
  - Traumatic wound care to prevent sepsis
  - Repair and restoration of genitourinary injury and tissue damage

HIGHLIGHTS

Novel Antimicrobial Hybrid Hydrogel Dressing Targeting Wound Infections Caused by Pan Drug Resistant (PDR) Bacterial Superbugs Resistant to All Current Antibiotics

Gauri Rao, Pharm.D., M.S., UNC Eshelman School of Pharmacy, University of North Carolina at Chapel Hill

Infections caused by PDR bacterial "superbugs," which are resistant to nearly all available antibiotics, are a significant cause of sepsis and death, particularly for Warfighters wounded in combat. Leveraging the resistance-proof, and long duration of action of teixobactins, a recently discovered class of antibiotics, Dr. Rao and her team aim to develop a durable and deployable wound dressing that delivers teixobactin-lipopeptide potentiator conjugates in a hydrogel form. This antibiotic hydrogel can be placed in a medic "tool-kit" for point-of-injury (POI) application. To date, the team has synthesized 127 of the proposed 150 novel teixobactin analogs and selected a number of promising candidates that display effective antibacterial activity against superbugs. International collaborators are optimizing the structure of the hydrogel scaffold to further improve its use in wound care. Success of this project, aligned to the FY19 Focus Area of scalable solutions for wound care, will not only result in resistance-resistant antimicrobial hydrogel dressing to prevent and treat wound infections caused by PDR bacterial superbugs, but will also provide medics the capability to provide immediate care at the POI.

EyeBOX Lens (EBLens): A Highly Portable Device for Assessment of mTBI in Deployed and Far-Forward Settings

Rosina Samadani, Ph.D., Oculogica, Inc.

mTBI and blast-related concussions affect cognitive function, overall performance, and put the Service Member and their team in danger when misdiagnosed and untreated. Current mTBI diagnoses are primarily based on clinical, subjective evaluation, which can lead to premature return to duty for Soldiers still experiencing deficits. In response to the FY20 Focus Area addressing solutions for assessment of mTBI, Dr. Samadani proposed to redevelop and ruggedize their FDA-approved EyeBOX test, which works by measuring binocular eye movements that correlate with cranial nerve function for unbiased, objective diagnosis of concussion far-forward and at the POI. The new technology, EBLens, is housed in a pair of rugged, lightweight, and ultra-low power eyeglasses. The eye-tracking device does not require expert medical knowledge to operate and has the potential to transform concussion diagnoses in combat environments, as well as civilian settings, allowing for immediate triaging to improve the effects of mTBI.

DUCHENNE MUSCULAR DYSTROPHY RESEARCH PROGRAM

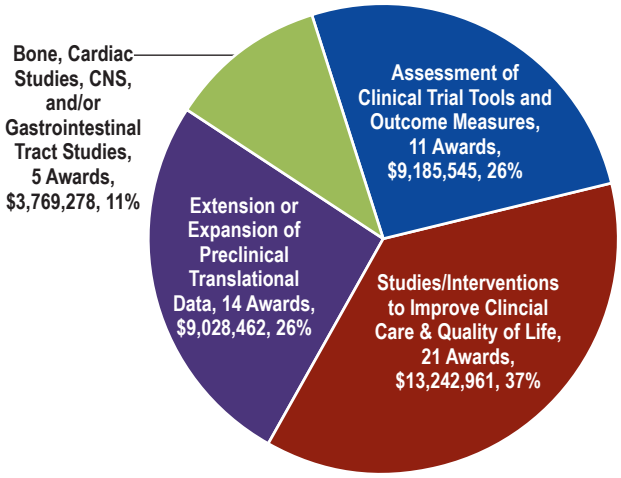
Vision: To preserve and improve the function and quality of life, and to extend the life span of all individuals with Duchenne

Mission: To better characterize Duchenne pathophysiology, support discovery and development of therapeutics, related devices and tools, as well as to promote their rigorous preclinical and clinical testing for the benefit of military beneficiaries and the general public

PROGRAM HISTORY

Duchenne muscular dystrophy (DMD) is the most common childhood form of muscular dystrophy, affecting approximately 1 out of every 3,600 to 5,000 male infants. Boys living with DMD experience devastating muscle weakness affecting the skeletal, heart, and respiratory muscles. Unfortunately, there is no cure for DMD, and muscle weaknesses progress to heart and respiratory failure, eventually lead to death before or during an individual's third decade.

In FY11, congressional appropriations established the Duchenne Muscular Dystrophy Research Program (DMDRP), and the program has received $49.6M in funding through FY21. The DMDRP has a research portfolio of 51 projects that includes studies on DMD's effects in areas such as bone, heart, and the central nervous system (CNS); research to improve clinical care and quality of life; assessment of clinical trial tools and outcome measures; and preclinical translational research to support therapeutic development. There is no treatment that can stop or reverse the progression of DMD. With the lack of any curative treatments, the DMDRP has placed its greatest emphasis on developing or improving treatments and clinical trial readiness.



FY11-FY20 DMDRP Dollars Invested per Focus Area
Total Investment: $35.2M

"What sets DMDRP apart from other grant programs is the diversity of input on research investment strategy. Patients, caregivers, foundations, and a diverse group of basic and translational researchers work together to shape both the future research priorities and the final funding recommendations. This unique process ensures that every research dollar is deployed in a way that will bring maximum impact to those currently living with Duchenne."

Laura Hagerty, Ph.D., ReveraGen BioPharma Inc., FY19-FY21 Programmatic Panel Member

2020 Congressional Appropriations, Research Investment, and Withholds and Management Costs

Congressional Appropriations	Research Investment	Withholds and Management Costs
$10M	Idea Development Award ..... $5,612,002 Translational Research Partnership Award $3,549,649	USAMRDC .....$66,300 SBIR/STTR .....$335,000 Mgt Costs (4.55%) $437,049
Total: $10M	**Total:** $9,161,651	**Total:** $838,349

FDA-APPROVED DRUGS IN THE MARKET

- Supported preclinical work that led to FDA approval of two therapeutics, Exondys 51 and Viltepso.® These therapeutics are currently available as potential treatments for over 20% of DMD patients who have mutations in exon 51 or exon 53.

Accelerating promising therapeutics into clinical applications:

- Dr. Sergio Villalta is exploring whether recombinant adeno-associated viral (rAAV) and dystrophin immunity impair the efficacy of gene therapy and determining if regulatory T cells can suppress this immunity. The results of this work are poised to develop a novel and effective immunoregulatory therapy that addresses the unmet need for a safer alternative to broad immunosuppression (i.e., chronic glucocorticoid therapy).
- In an effort to improve the efficacy of antisense oligonucleotide (AO) therapy for dystrophin restoration, Dr. Jyoti Jaiswai is exploring the use of AOs to simultaneously lower transforming growth factor (TGF) and increase dystrophin production, providing a novel all AO-based tool that will enhance the efficacy of current AO-based therapies for DMD, while simultaneously enhancing muscle regeneration and reducing fibrotic muscle degeneration.

Assess clinical trial tools and outcome measures:

- In a collaborative project, Drs. Rebecca Willcocks and Chamith Rajapakse are developing non-invasive magnetic resonance measures of bone quality in individuals with DMD as biomarkers that will facilitate both fracture treatment and fracture prevention trials in DMD, including trials of existing and novel bone-targeted therapies and muscle-targeted therapies that may improve bone.
- Dr. Yetrib Hathout established a new prognostic test that is currently being tested by biopharma companies to measure levels of dystrophin in muscle biopsies collected from pre- and post-treated DMD patients enrolled in clinical trials using dystrophin replacement therapies.

Assess Duchenne's effect on bone, heart, CNS, and the GI tract:

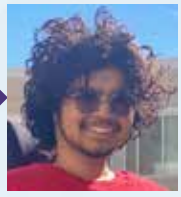
- Dr. Holly Colognato is studying which dystrophins regulate postnatal brain development, establish the "critical window" for dystrophin restoration in the brain, and determine whether dystrophin-replacement therapies can improve cognitive function in DMD.

Improve clinical care and quality of life:

- Supporting preclinical studies on the development of a novel office-based injectable of relaxin-2 to treat Duchenne-related fibrosis by Drs. Edward Ahn and Ara Nazarian, and the results of these studies will be used to support an IND application to the FDA.

"When I was nominated to serve as a consumer reviewer for DMDRP I was elated – primarily because I would be able to continue on in my pursuit to help the DMD community, and also because I was fascinated to learn more about all the cool science in the pipeline. While I was initially intimidated by writing critiques that would be read by Ph.D.s, I began to eventually have fun writing in a scholarly tone and sharing my views as a potential future user of certain treatments.... Everyone was receptive to my thoughts and opinions, giving me the chance to provide insights that could actually be useful."

Yuva Gambhir, CureDuchenne, FY20 Consumer Peer Reviewer



EPILEPSY RESEARCH PROGRAM

Vision: A time when post-traumatic epilepsy can be prevented or optimally managed

Mission: To understand the mechanisms of post-traumatic epilepsy and associated comorbidities to improve quality of life, especially in Service Members, Veterans, and caregivers

PROGRAM HISTORY

Congress established the Peer Reviewed Epilepsy Research Program (ERP) in FY15 in response to concerns about the long-term consequences of TBIs. Any type of head injury increases the risk for a seizure. When these seizures become frequent, individuals are diagnosed with post-traumatic epilepsy (PTE). While there are treatments that effectively treat PTE, individuals who sustain TBIs are still at risk for breakthrough seizures, which can be fatal.

The ERP imagines a time when PTE can be prevented or optimally managed. Prevention involves understanding the genesis and mechanisms of post-traumatic seizures. This involves a strategy of innovations in seizure diagnosis, an improved understanding of how TBI interacts with other epilepsy-related risk factors, and ultimately the development of novel interventions that will stop seizures from evolving into epilepsy. Not all cases of PTE will be prevented. For individuals who progress to PTE, the ERP also supports multiple strategies aimed at advancing symptom management and care. Having a better understanding of the current state of PTE care will help identify solutions to improve the daily lives of individuals and caregivers living with this debilitating disorder.

The ERP funded 49 research projects since its inception, which examine a wide range of topics. Areas of inquiry focus on gaps in knowledge of PTE such as the development of new and innovative PTE models, differences between PTE and psychogenic non-epileptic seizures, functional brain changes associated with PTE, and epidemiological studies of Service Members.

FOCUS AREAS

While the history of PTE research extends back to World War I, much less is known about PTE in military populations who have served in current conflicts. Increased awareness and understanding of the consequences of mild, moderate, and repetitive head injuries has led to new questions regarding TBI and its subsequent long-term consequences, such as PTE. The ERP continually monitors the research landscape and has identified five major gaps in our knowledge of PTE. All of the gaps address major research areas that will allow the program to address its mission and ultimately its vision. There is a strong need for innovative research such as technologies that will improve how PTE research can be conducted. Other areas will advance our understanding of markers and mechanisms of PTE, so that the basis of PTE can be understood and new ideas can be developed toward prevention. The ERP also supports epidemiological studies. These are data-based studies that are used to develop a comprehensive profile of individuals living with PTE, to include care management. The ERP also funds prospective, longitudinal studies with a focus on improving prognosis and diagnosis. The ERP also funds research to understand and improve the quality of life of individuals with living PTE, their families, and their caregivers, such as how PTE impacts daily living.

"The ERP honors my husband's Service and sacrifice by its mission; to better understand how trauma transforms the brain and disturbs cognitive function. This program is tasked to find and eliminate mechanisms that start the epileptogenic process, which means a better chance for survival, rehabilitation, and quality of life for the next generations of Veterans."

Patricia Horan, CURE Epilepsy, FY18-FY21 Programmatic Panel Member

2020 Congressional Appropriations, Research Investment, and Withholds and Management Costs

Congressional Appropriations	Research Investment	Withholds and Management Costs
$12M	Idea Development Award ..... $3,573,020 Quality of Life Research Award ..... $727,067 Research Partnership Award $6,199,990	USAMRDC ..... $231,940 SBIR/STTR .....$403,000 Mgt Costs (7.61%).....$864,983
Total: $12M	**Total:** $10,500,077	**Total:** $1,499,923

ERP strives to fund innovative and impactful research to understand the magnitude of post-traumatic epilepsy and improve patient care and outcomes.

Leveraging Existing Studies to Advance PTE Research: The TRACK-TBI Epileptogenesis Project

Ramon Diaz-Arrastia, M.D., Ph.D., University of Pennsylvania

In order to advance clinical neuroscience, both basic and translational research are needed. Consortia such as the Alzheimer's Disease Neuroimaging Initiative, Concussion Assessment, Research, and Education Consortium (CARE), and The Long-Term Impact of Military-Relevant Brain Injury Consortium (LIMBIC) have all investigated different perspectives of the long-term consequences of head injuries. Each uses a systematic and harmonized approach across multiple research sites in order to generate datasets that have a common architecture. These types of approaches allow investigators from both inside and outside the consortia to ask big questions and get answers that require large numbers of patient-centered data points. Researchers from the University of Pennsylvania, the University of California, San Francisco, the University of Pittsburgh, and the University of California, San Diego came together to form a consortium to answer several important questions in PTE research. They used the Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK-TBI) consortium as the backbone for the PTE study. This allowed the researchers to start working with a pre-existing cohort of more than 2,600 individuals with TBI. This will allow the researchers a longer time to observe these individuals for signs of PTE, as opposed to recruiting a new cohort. Beyond understanding health outcomes that are studied in other research initiatives, this effort will look at the brain networks that are disrupted in PTE. This approach may lead to novel diagnostics that can only be studied in large patient cohorts. By leveraging existing clinical infrastructure and patient cohorts, this approach provides hope to impact patient care in a cost-effective, synergistic, and accelerated manner.

"The TRACK-TBI study is the first study that has enrolled a sufficient sample size of mild TBI subjects with sufficiently granular clinical and biomarker information to allow a prospective assessment of the mechanistic underpinnings of PTE after mild and moderate TBI, which will likely overlap but differ in important aspects from PTE arising after severe TBI."
Dr. Ramon Diaz-Arrastia

Quality of Life Research for PTE

Barbara C. Jobst, M.D., Dr. Med, FAAN, FAES, Dartmouth-Hitchcock Medical Center
Elaine T. Kiriakopoulos, M.D., MSc, Dartmouth-Hitchcock Medical Center

PTE, even when effectively treated with current anti-seizure therapies, can present other symptoms that make the management of daily life activities difficult. Memory and behavioral challenges can put some independent daily activities out of reach for individuals living with PTE. PTE can also place unique demands on family members, which can strain relationships. Strategies to alleviate or stabilize PTE symptoms, therefore, have the potential to strengthen relationships and allow individuals to once again enjoy activities that used to be part of their everyday lives, such as work or volunteering.

One potential intervention recently funded by the ERP is called HOBSCOTCH (HOme-Based Self-management and COgnitive Training CHanges Lives). HOBSCOTCH is a behavioral program that provides epilepsy education, problem-solving skills, self-awareness training, compensatory memory strategies, and quick relaxation exercises to assist patients with memory and cognitive challenges. One of its great advantages is that it does not require a classroom setting. Participants can complete the intervention by telehealth in the comfort of their homes or other familiar surroundings.

Dr. Barbara Jobst of the Dartmouth-Hitchcock Medical Center has studied HOBSCOTCH in individuals living with epilepsy. In this study, Dr. Jobst and her research team will examine, for the first time, whether HOBSCOTCH is effective in individuals living with epilepsy and cognitive challenges they acquired after TBI. The study will also assess potential quality of life and health benefits for caregivers, as they will participate in the education and relaxation components of the HOBSCOTCH program. Dr. Jobst envisions that both the patient and caregiver's perspectives will be particularly critical to developing the patient/family education that accompanies the HOBSCOTCH PTE study intervention.

"HOBSCOTCH is a program that may enable patients and Veterans with traumatic brain injury to address their memory problems by empowering them and their caregiver to cope with their memory disability."
Dr. Barbara C. Jobst

GULF WAR ILLNESS RESEARCH PROGRAM

Vision: Improved health and lives of Veterans who have Gulf War Illness

Mission: Fund Gulf War Illness research that expeditiously identifies effective treatments and accelerates their clinical application, improves definition and diagnosis, and results in better understanding of pathobiology and symptoms of disease

PROGRAM HISTORY

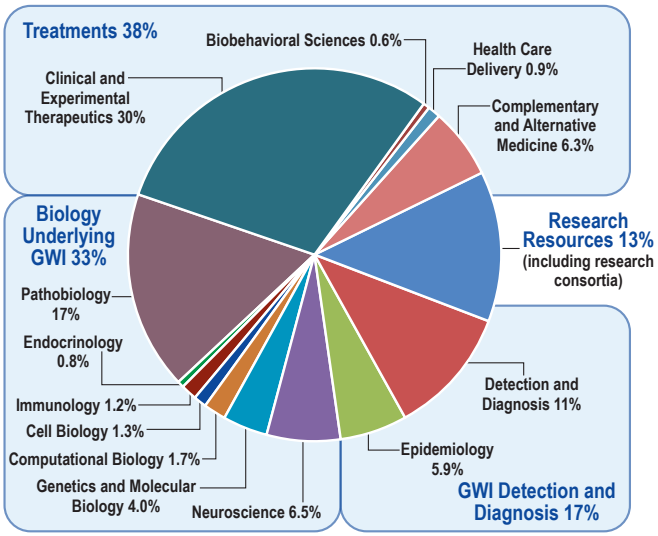
Congress established the Peer Reviewed Gulf War Illness Research Program (GWIRP) in 2006 and renewed it in 2008 as a result of Gulf War Veteran advocacy and congressional support. GWIRP-funded research plays a leading role in the fight against Gulf War Illness (GWI) by challenging scientists to explore new paradigms and by emphasizing research that will accelerate the translation of promising ideas to application in the clinic. While fostering research across the GWI research landscape, the program maintains a primary focus on treatments and prioritizes expansion, replication, and comparative studies critical for FDA approval of new treatments and acceptance of new therapeutic protocols into general practice. GWIRP-funded mechanisms also promote synergistic collaborations across disciplines, encourage scientists outside of the GWI community to apply their expertise to questions in GWI, and integrate Gulf War Veterans and scientists in unique and meaningful research partnerships to improve program focus and impact.

Continued Veteran advocacy, together with program accomplishments, has resulted in more than $200M in congressional appropriations through FY20. The GWIRP portfolio includes over 200 research projects spanning investigations of basic pathobiology of GWI to trials of pharmaceuticals and other therapies. The pie chart shows the distribution of funding addressing different research areas of GWI research.

OVERARCHING CHALLENGES

Considering the current GWI landscape and the GWIRP's mission, the program supports research that address the following Overarching Challenges:

- **Treatments:** Eliminate the health consequences associated with GWI and/or revolutionize treatment.
- **Diagnosis:** Better define and diagnose GWI.
- **Subtyping:** Distinguish subtypes to better target treatments, or monitor therapy, or identify severity of GWI, or why GWI is worse for some Veterans than for others.
- **Determinants:** Identify and validate determinants of GWI, latency, and impacts on organs and systems.
- **Consequences:** Determine whether GWI alters risk for developing neurological conditions, cancers, or other serious conditions, or whether GWI alters outcomes of other infections/diseases.
- **Communicate and Educate:** Help Veterans, their caregivers, and clinicians communicate effectively about GWI, its symptoms, and potential treatments.



FY06–FY20 GWIRP Portfolio Investment by Research Area

2020 Congressional Appropriations, Research Investment, and Withholds and Management Costs

Congressional Appropriations	Research Investment	Withholds and Management Costs
$22M	Clinical Evaluation Award ..... $3,820,101 Idea Award ..... $1,834,210 New Investigator Award ..... $2,693,845 Research Advancement Award ..... $8,422,302 Modifications to ongoing awards $3,108,161	USAMRDC ..... $425,860 SBIR/STTR ..... $707,000 Mgt Costs (4.74%) $988,521
Total: $22M	**Total:** $19,878,619	**Total:** $2,121,381

GWIRP-funded treatment research has included 33 clinical trials. Of these, 13 are actively recruiting or coming online in the near future. Links to GWIRP clinical trials are available at *https://cdmrp.army.mil/gwirp/clinical_trials/GWIRPsct*

2020 DOD-VA JOINT GULF WAR ILLNESS STATE OF THE SCIENCE (GWI SOTS) CONFERENCE

In August 2020, a first-ever GWI SOTS conference was co-hosted by the GWIRP and the VA, Office of Research and Development. This conference coincided with the 30-year anniversary of the start of the 1990-1991 Gulf War, Operation Desert Shield, and created a forum for Gulf War Veterans to engage directly with scientists and learn about the studies that are being conducted to further understand and treat the disease. Conference presentation highlights are shown below.

PLENARY SESSION HIGHLIGHTS

Plenary Session D – Treatments

Low Glutamate Diet
Kathleen F. Holton, James N. Baraniuk, et al
In a clinical pilot study of a low-glutamate/whole foods diet, Veterans with GWI were trained to avoid foods high in glutamate. After 1 month, participants reported reductions in pain, fatigue, sleep, memory, and gastrointestinal symptoms.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7551234/

Plenary Session G – Epidemiology

Patterns of Illness in Female Gulf War Veterans
Kimberly Sullivan, Steven S. Coughlin, et al
This study of women Gulf War Veterans indicates that rates of multiple symptoms are double the rate of female non-deployed counterparts, demonstrating that GWI remains a serious chronic health issue for women.
https://www.liebertpub.com/doi/pdf/10.1089/jwh.2019.7705

Plenary Session I – Definition and Diagnosis-Biomarkers

Plasma Autoantibodies for Specific Diagnosis of GWI
Mohamed B. Abou-Donia, Kimberly Sullivan, et al
This study expands and validates prior results showing that plasma levels of specific autoantibodies to nervous system proteins can be used as a marker to distinguish Veterans with GWI from Veterans suffering from other disorders that have similar symptoms.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7563126/

Plenary Session L – Pathobiology (Brain)

Imaging Neuroinflammation in Veterans with GWI
Zeynab Alshelh, Marco L. Loggia, et al
Positron emission tomography (PET), using a specific radioactive tag to visualize activation of glial cells and astrocytes, revealed elevated inflammation in brains of Veterans and could be used as a marker of GWI.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7864588/

"The Veterans with GWI who served our country deserve answers and treatments that only research can provide. I'm honored to be a part of the GWIRP and to help to identify research that will make a difference in their lives."
Vicky Whittemore, Ph.D., National Institute of Neurological Disorders and Stroke, FY20-FY21 Programmatic Panel Chair

"As the world changes with the recent pandemic, it is more evident the importance of research. Being an advocate and consumer reviewer for Veterans who suffer from GWI as part of the CDMRP team has helped open many doors and answer questions for me and other Veterans. There is a real sense of satisfaction while sitting among some of the top research doctors in the U.S. during the review meeting and knowing they are listening to every word you have to say – where your opinion matters. The best part is that the Veteran voices are being heard and not just falling to the wayside."
William "Bill" Watts, South Florida VA Foundation for Research and Education, FY18-FY19, FY21 Consumer Peer Reviewer

HEARING RESTORATION RESEARCH PROGRAM

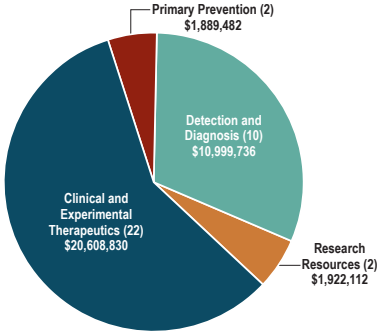
Vision: Improve the operational performance/effectiveness, medical readiness, and quality of life of Service Members and Veterans with auditory system injuries

Mission: Advance the science of hearing restoration by delivering groundbreaking research and solutions that remove barriers to the successful treatment of auditory system injury

PROGRAM HISTORY

Congress initiated the Peer Reviewed Hearing Restoration Research Program (HRRP) in 2017 to pursue promising, necessary research for treatment of burdensome and very prevalent auditory system injury.

More than 30 million Americans over the age of 12 have hearing loss in both ears, and an estimated 48 million have hearing loss in at least one ear. While hearing loss has profound impact on quality of life, there is no drug approved by the FDA for hearing restoration. Despite significant advances in the understanding of hearing loss in animal models, the development of hearing restoration therapeutics has been hindered by difficulties in validation and translation and by limitations in precision diagnostic capability. The HRRP aims to advance the science of hearing restoration by funding groundbreaking research that removes barriers in translation and diagnosis.



FY17-FY20 HRRP Portfolio Investment by SCS Code

RELEVANCE TO MILITARY HEALTH

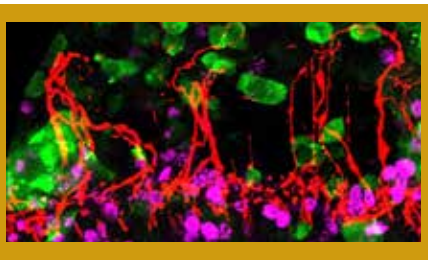
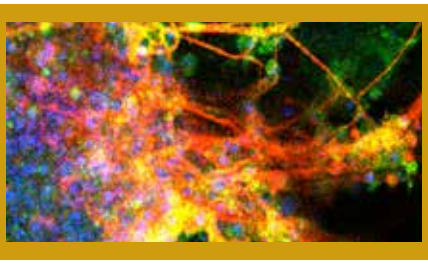
Service Members face high risks of noise-induced hearing loss and auditory system injury, including the potential for hidden hearing loss (e.g., cochlear synaptopathy). Service Members are exposed to high levels of noise unique to military operating and training environments (e.g., gunshots, helicopters, explosions, aircraft take-offs from carrier decks). In contrast with exposure to noise in construction, agriculture, and recreation, encountering combat noise is not predictable. Protection against combat noise is further complicated by the need for Warfighters to hear sound and to communicate. Furthermore, Service Members often operate in austere/remote environments without access to a fixed or mobile medical facility and where diagnostic and treatment resources and medical personnel are unavailable or limited for extended periods of time. Data from the VA Veterans Benefits Administration indicate that the two most prevalent Service-connected disabilities are related to hearing disorders, with more than 1.3 million Veterans suffering from hearing loss.

FOCUS AREAS

- Accelerate translation of biological regeneration/repair mechanisms into therapies that treat auditory system injury and restore auditory function.
- Diagnostic tests that help differentiate sensory, neural, synaptic, and central processing disorders that may inform applicability and outcomes for current or future hearing restoration therapeutics.
- Develop reliable in vitro human models to facilitate the understanding, derivation, and characterization of human auditory cells and/or to facilitate the evaluation of hearing restoration therapies.
- Develop and/or validate techniques/methods beyond the audiogram to diagnose acute auditory system injury in austere or remote environments.

2020 Congressional Appropriations, Research Investment, and Withholds and Management Costs

Congressional Appropriations	Research Investment	Withholds and Management Costs
$10M	Focused Research Awards - Funding Level 1 ..... $2,447,288 Focused Research Award - Funding Level 2 ..... $6,145,643	USAMRDC ..... $193,300 SBIR/STTR ..... $335,000 Mgt Costs (9.28%) $878,769
Total: $10M	**Total:** $8,592,931	**Total:** $1,407,069


RECENT ACHIEVEMENTS FROM HRRP-FUNDED RESEARCH

Stem Cell Regeneration of Human Spiral Ganglion Neurons Toward Hearing Restoration

Akihiro J. Matsuoka, M.D., Ph.D., Northwestern University

Dr. Akihiro J. Matsuoka received an FY17 Translational Research Award to develop a biohybrid cochlear implant that overcomes what is known as the electrode-neuron gap in existing implants. The research team successfully derived three-dimensional (3D) otic progenitor spheroids from human embryonic cells.[1] Combining the spheroids with a nanostructured hydrogel, they engineered an artificial 3D stem cell niche that enhances the survival and neuronal differentiation of transplanted otic neuronal progenitors.[2] This is a major step toward bridging the electrode-neuron gap. Additionally, the creation of an engineered stem cell niche has significant implications to stem cell-based treatment of sensorineural hearing loss.

Identifying the Sources of Degraded Speech-in-Noise Understanding and Individualized Therapeutic Options

Inyong Choi, Ph.D., University of Iowa

Understanding speech in noisy environments is a complex process requiring multiple neural processes. The ability to understand speech-in-noise degrades severely in patients of hearing loss. Funded by an FY18 Focused Applied Research Award, Dr. Inyong Choi and team identified two neural subsystems that contribute to speech-in-noise understanding: a sensory gain control subsystem that attenuates neural representation of background noise and another, independent, speech recognition subsystem that extracts information from speech sounds.[3] The mechanistic insight into speech-in-noise understanding will facilitate the development of improved assessment of Service Members' auditory fitness for duty.

Modulating the Cochlear Proteostasis Network to Prevent Hidden Hearing Loss

Jeffrey Savas, Ph.D., Northwestern University

Dr. Jeffrey Savas received an FY18 Focused Applied Research Award to investigate the cochlear proteostasis network as potential therapeutic target for hidden hearing loss. The research team has recently completed a quantitative proteomic and transcriptomic study of the effect of noise insult on mouse cochlea.[4] The results demonstrated, for the first time, exposure to loud noise causes cochlear proteotoxicity. They went on and identified and confirmed hundreds of proteins that accumulate, including cytoskeletal proteins, and several nodes of the proteostasis network. Transcriptomic analysis reveals that a subset of the genes encoding these proteins also increases acutely after noise exposure, including numerous proteasome subunits. Notably, global cochlear protein ubiquitylation levels also build up after exposure to excess noise. After 2 weeks of recovery, they found that the cochlea selectively elevates the abundance of the protein synthesis machinery. Ultimately, this groundbreaking work opens the door for the identification and characterization of many therapeutic targets.

"Serving and representing Veterans and their family members was the opportunity of a lifetime. I was able to help researchers see the human side of hearing loss and the impact it has on entire families. The first time I heard of hidden hearing loss was when I sat on a research panel. That's when I learned that the reason I could not hear conversations in a noisy room was hidden hearing loss; before that I had been told that it was due to 'panic attacks' due to my PTSD. Learning this has had a huge impact on my life, and I am no longer afraid to go to crowded places. Now I know why multiple PTSD medications did nothing to help me. It changed my life."

David Steeley, Heart of Texas Veterans One Stop, FY19-FY20 Consumer Peer Reviewer

[1] Heuer RA, Nella KT, Chang HT, et al. 2020. Three-dimensional otic neuronal progenitor spheroids derived from human embryonic stem cells. *Tissue Eng Part A.* 27(3-4):256-269.

[2] Chang HT, Heuer RA, Oleksijew AM, et al. 2020. An engineered three-dimensional stem cell niche in the inner ear by applying a nanofibrillar cellulose hydrogel with a sustained-release neurotrophic factor delivery system. *Acta Biomater.* 108:111-127.

[3] Kim S, Schwalje AT. Liu AS, et al. 2021. Pre- and post-target cortical processes predict speech-in-noise performance. *NeuroImage.* Vol. 228:117699.

[4] Jongkamonwiwat N, Ramirez MA, Edassery S, et al. 2020. Noise exposures causing hearing loss generate proteotoxic stress and activate the proteostasis network. *Cell Rep.* 33(8):108431.

JOINT WARFIGHTER MEDICAL RESEARCH PROGRAM

Vision: Move military relevant medical solutions forward in the acquisition life-cycle to meet the needs of Service Members and other military health system beneficiaries

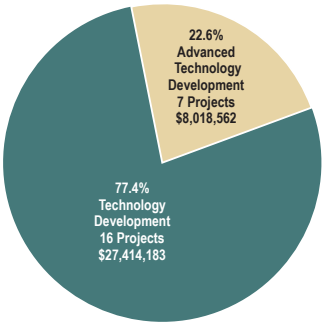
Mission: Accelerate research and development projects that have the potential to close high priority Department of Defense medical capability gaps

PROGRAM HISTORY

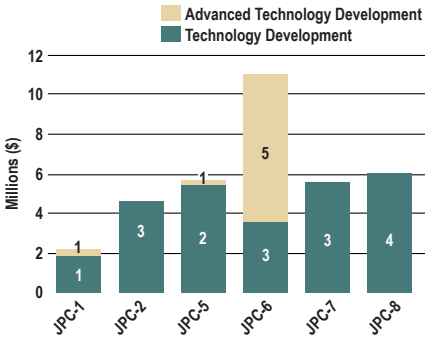
The Joint Warfighter Medical Research Program (JWMRP) provides the DOD with a powerful tool for advancing previously funded Congressional Special Interest and core program funded medical research and development projects that address military medical requirements of the Services while complementing and enhancing DMRDP. The JWMRP leverages the efforts of industry and academia for projects that show promise in closing identified military medical capability gaps and provides the funding to move these products through the developmental process.

Each year, a broad spectrum of research projects are considered for funding under JWMRP. The projects align to the six JPCs scientific domains represented in DMRDP, including Medical Simulation and Information Sciences, Military Infectious Diseases, Military Operational Medicine, Combat Casualty Care, Radiation Health Effects, and Clinical and Rehabilitative Medicine.

Congress first appropriated $50M for JWMRP in FY12 and again in FY13; later doubling the appropriation to $100M in FY14, followed by $50M per fiscal year in FY15-FY19 and $40M in FY20-FY21. Because the overall goal of the program is to deliver a product for the DOD, the proportion of funding available for advanced technology development initiatives has increased over the years. The JWMRP funded a total of 28 projects in FY12, 35 in FY13, 46 in FY14, 30 in FY15, 34 in FY16, 27 in FY17, 17 in FY18, 13 in FY19, and 23 in FY20. The graph on the right, below, depicts the program investments for FY20. The JWMRP is a dynamic program that facilitates maturation of previous congressionally and core programmed funded efforts that demonstrate the potential to close identified military medical capability gaps. By focusing on both early and advanced technology development, the JWMRP provides a pathway to transition products to military healthcare providers and the Warfighter.



FY20 JWMRP Investment (% of total)



FY20 JWMRP Final Funding Distribution (Number of Awards Granted Indicated in Each Bar Chart)

"Since 2012, the JWMRP has augmented DOD and Service efforts to develop materiel products to meet medical requirements. It has provided the opportunity to bring solutions forward more expeditiously – both for prior initiatives close to achieving their objectives, and for existing materiel acquisition programs. Sponsored efforts encompass drug and vaccine development, device development, clinical trials, and research seeking knowledge in support of clinical practices. This program is a powerful tool in advancing medical product development to support our Armed Forces."

Col Patricia A. Reilly (U.S. Air Force, retired), Ph.D., Program Director, Defense Health Program Advanced Development & Transition Office of the Principal Assistant for Acquisition, USAMRDC, FY15-FY21 Programmatic Panel Member

2020 Congressional Appropriations, Research Investment, and Withholds and Management Costs

Congressional Appropriations	Research Investment	Withholds and Management Costs
$40M	Peer-Reviewed Research ..... $30,315,913 Modifications to ongoing awards..... $5,116,832	USAMRDC .....$774,606 SBIR/STTR ..... $1,330,000 Mgt Costs (6.16%) $2,462,649
Total: $40M	**Total:** $35,432,745	**Total:** $4,567,255

ACCELERATING THE DEVELOPMENT OF MILITARY MEDICAL SOLUTIONS

Technology Readiness Level

4

- Accelerating development of freeze-dried plasma in a combat ready rugged lightweight container
- IND-enablement of Kinocidin Gamma-RP-1 for multidrug-resistant gram-negative infections
- Development of BIO301 as an oral prophylactic and post-exposure treatment for acute radiation syndrome
- MeniscoFix total meniscus replacement device

- Open Medical Gesture combat medic interactions for VR and mixed-reality tactical stimulations
- Phase 1a clinical trial of anti-ceramide single-chain variable fragment for radiation GI syndrome prophylaxis
- Development of a novel product for temporary corneal repair

5

- AccuPump™ infusion pump module for the delivery of drugs, fluids, and blood products at point of injury
- Phase 1 clinical trial for a direct acting polymyxin antibiotic to treat multidrug resistant gram-negative pathogens
- Phase 1/2 clinical trial of bacteriophage for treatment of bacterial infections
- Vital Wave noncontact vital signs monitor

- Multi-site clinical trial of a neural-enabled prosthetic hand system
- PleuraPath™ chest tube for thoracostomy

6

- Ultrasound for assessing critical head trauma
- Multicenter implementation trial of targeted normoxia strategy to inform oxygen requirements for combat casualty care

8

- PfSPZ vaccine to protect the Warfighter from malaria

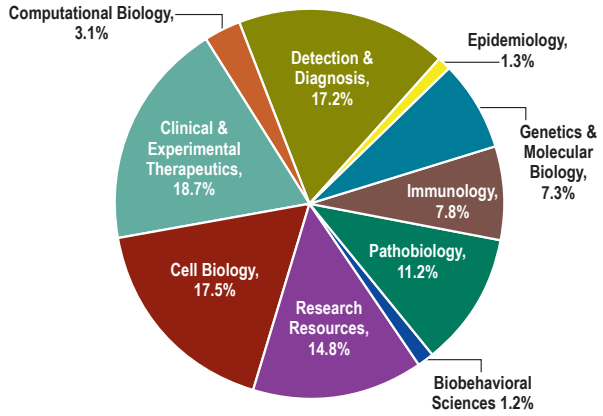
KIDNEY CANCER RESEARCH PROGRAM

Vision: To eliminate kidney cancer through collaboration and discovery

Mission: To promote rigorous, innovative, high-impact research in kidney cancer for the benefit of Service Members, Veterans, and the American public

PROGRAM HISTORY

Efforts by kidney cancer advocates, along with congressional support, led to the establishment of the Peer Reviewed Kidney Cancer Research Program (KCRP) in 2017. The KCRP has received $135M in congressional appropriations through FY21. Through offering and funding more than 142 research awards, the KCRP has invested in innovative research, translational studies, clinical research collaborations, technology advancement, and training the next generation of clinicians, clinical trial nurses, and researchers.



FY17-FY20 Funds Allocated to Awards According to Research Area

KCRP OVERARCHING STRATEGIC GOALS

- Increase understanding of the biology of kidney cancer
- Develop novel therapeutic strategies for the treatment of kidney cancer
- Improve patient care for kidney cancer
- Grow the field and increase collaboration in the area of kidney cancer

KIDNEY CANCER RELEVANCE TO MILITARY HEALTH

Tobacco smoking, environmental and occupational exposures are some of the factors known to increase an individual's risk of developing kidney cancer.[1] With incidences of smoking more prevalent in Service Members and Veterans than in civilian populations, and a higher chance of exposure to chlorinated solvents, petrochemicals, and heavy metals associated with increased risk of renal cell carcinoma,[2,3] kidney cancer is especially relevant to the military.

MILITARY HEALTH SYSTEM DATA (2010-2019)

- 911 Active Service Members diagnosed with kidney cancer (n = 603) and/or renal pelvis cancer (n = 65) through the MHS
- 50,128 Other DOD beneficiaries diagnosed with kidney cancer (n = 48,869) and/or renal pelvis cancer (n = 6,012) through the MHS

2020 Congressional Appropriations, Research Investment, and Withholds and Management Costs

Congressional Appropriations	Research Investment	Withholds and Management Costs
$40M	Academy of Kidney Cancer Investigators - Early Career Investigator Award ..... $3,616,259 Clinical Consortium Award ..... $1,457,786 Clinical Research Nurse Development Award ..... $531,000 Concept Award ..... $2,351,749 Idea Development Award ..... $17,872,107 Postdoctoral and Clinical Fellowship Award ..... $1,898,418 Translational Research Partnership Award ..... $4,942,621 Modifications to ongoing awards..... $3,132,974	USAMRDC ..... $773,180 SBIR/STTR ..... $1,341,000 Mgt Costs (5.5%)..... $2,082,906
Total: $40M	**Total:** $35,802,914	**Total:** $4,197,086

[1] Safiri S, Kolahi AA, Mansournia MA, et al. 2020. The burden of kidney cancer and its attributable risk factors in 195 countries and territories, 1990-2017. *Sci Rep* 10(1):13862. https://doi.org/10.1038/s41598-020-70840-2

[2] https://www.publichealth.va.gov/exposures/categories/occupational-hazards.asp

[3] https://www.va.gov/disability/eligibility/hazardous-materials-exposure/camp-lejeune-water-contamination/

SANDY BARKER, CONSUMER ADVOCATE AND KCRP CONSUMER PEER REVIEWER

Sandy Barker served as an FY18 consumer peer reviewer for the KCRP, representing the Kidney Cancer Action Network. Sadly, in early 2020, Sandy lost her battle with kidney cancer, but she made an impact that is lasting. Caroline Sample,[4] who also served as a KCRP consumer peer reviewer, honored Sandy with a Moment of Silence at the KCRP's FY20 Peer Review meeting. Caroline and Sandy bonded through their shared experiences with Interleukin-2 therapy and their service as peer reviewers to help bring the patient perspective to the research process. "[Sandy Barker] wanted to learn all she could about the disease that ultimately ended her life. She was a sponge for knowledge. She often knew more than her nurses about upcoming treatment developments. She shared that knowledge generously with the SmartPatients community. She participated in the CDMRP Kidney Cancer Research Program as a consumer reviewer. Two years ago she was here, one of us. Last year she was too sick to participate. We all miss her."

Excerpted from FY20 KCRP Peer Review Moment of Silence, Caroline Sample, Programmatic Panel Consumer Advocate

RESEARCH HIGHLIGHTS ADDRESSING KCRP STRATEGIC GOALS

Increase Understanding of the Biology of Kidney Cancer

Stromal β-Catenin Activation Contributes to Abnormal Kidney Formation in Mice That Mimics Human Wilms Tumor

Keri A. Drake, M.D., University of Texas, Southwestern Medical Center at Dallas

Nephron progenitor cells (NPCs) normally differentiate into tubules that form nephrons. In the childhood cancer called Wilms Tumor (WT), the NPCs persist in an immature state where they keep dividing and create tumors that sometimes contain pieces of bone. Dr. Drake and the research team at UT Southwestern knew that excess activation of a molecule called β-catenin was often found in WT. With the support of a KCRP FY18 Physician Research Award, the research team investigated the effect of excess β-catenin activation on the maturation of NPCs. In experiments in mice, they elevated excess β-catenin activation in the NPCs or in the stroma surrounding the NPCs or both. Excess β-catenin resulted in disruption of the normal pattern of NPC maturation and tubule development, and in the case of elevation in both NPCs and stroma, actual growth of pieces of bone in the kidney. Thus, the research team has found strong evidence for a link between activation of β-catenin and WT pathogenesis. This gives researchers a new avenue to explore for WT treatments by finding molecules that reduce β-catenin activation or ameliorate its effects on cellular processes.

Publication:

Drake KA, Chaney CP, Das A, et al. 2020. Stromal β-catenin activation impacts nephron progenitor differentiation in the developing kidney and may contribute to Wilms tumor. *Development* 147(21):dev189597. https://journals.biologists.com/dev/article/147/21/dev189597/226408/Stromal-catenin-activation-impacts-nephro

Develop Novel Therapeutic Strategies for the Treatment of Kidney Cancer

Profilin 1 Promotes Aggressiveness of ccRCC and Provides a Potential New Therapeutic Target

Partha Roy, Ph.D., University of Pittsburgh

Clear cell renal cell carcinoma (ccRCC) represents the most commonly diagnosed subtype of kidney cancer. Features of ccRCC include loss of the tumor-suppressing gene called "Von-Hippel Lindau" (VHL) and a markedly vascularized tumor microenvironment. Dr. Partha Roy and his team at the University of Pittsburgh sought to exploit this vasculature as a target. With support from an FY18 KCRP Idea Development Award - Established Investigator, his team analyzed data from the Cancer Genome Atlas and found that expression of profiling 1 (Pfn1) in ccRCC tumors was strongly associated with poor prognosis, so they studied what Pfn1 did on ccRCC. In RCC cell lines deficient in VHL, they found that removing Pfn1 reduced proliferation and migratory behavior (hallmarks of cancer cells), while elevating it caused the cells of the vasculature to export Pfn1 and deposit it in the growth media. Pfn1 normally interacts with the cell actin cytoskeleton, so the group developed a small molecule inhibitor that disrupts the Pfn1-actin interaction. They found that treating RCC cells with C47 reduced migration and proliferation, and injecting mice bearing ccRCC tumors with C47 resulted in a significant reduction of tumor size without discernible weight loss or other side effects. Dr. Roy's work has the potential to translate into a promising new therapy to improve outcomes for patients diagnosed with ccRCC.

Publication:

Allen A, Gau D, Francoeur P, et al. 2020. Actin-binding protein profilin1 promotes aggressiveness of clear-cell renal cell carcinoma cells. *Journal of Cell Biology* 295(46):P15636-15649. https://www.jbc.org/content/295/46/15636

[4] https://kccure.org/2019/05/voice-of-kidney-cancer-caroline-sample/

LUNG CANCER RESEARCH PROGRAM

Vision: To eradicate deaths and suffering from lung cancer to better the health and welfare of Service Members, Veterans, and the American public

Mission: Support and integrate research from multiple disciplines for risk assessment, prevention, early detection, diagnosis, and treatment for the control and cure of lung cancer

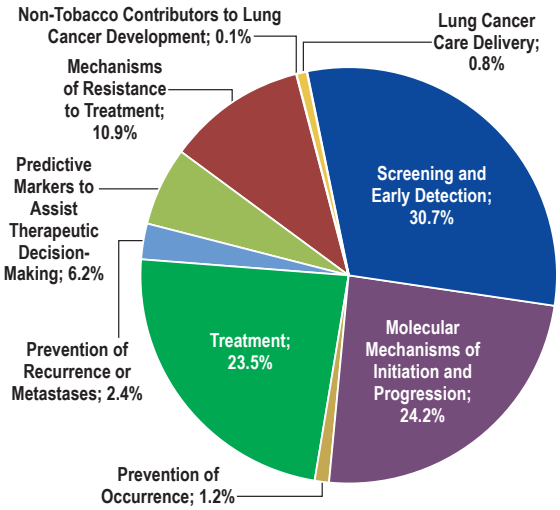
PROGRAM HISTORY

A congressional appropriation of $20M established the Peer Reviewed Lung Cancer Research Program (LCRP) in FY09, and it has received a total of $175.5M through FY21. The LCRP has played a critical role in helping to accelerate high-impact translational research, encourage innovation and stimulate creativity, bring new investigators into the lung cancer field, and facilitate the creation of unique partnerships and resources.

Several factors have been shown to contribute to the development of lung cancer, particularly smoking and exposure to environmental carcinogens being the most prevalent; however, 10%-15% of lung cancers occur in people who are non-smokers. Lung cancer risk for our military is significant, as an estimated 24%-38% of Service Members are smokers, compared to 14% of civilians.[1] Among military Veterans, 29% reported current tobacco use,[2] and an estimated 900,000 Veterans remain at risk due to age, smoking, and other environmental exposures during and after military Service. The impact and burden on the MHS is demonstrated by hospital encounters; during 2010-2019 there were over 2.7 million outpatient encounters and more than 450,000 hospital bed days for lung cancer by various DOD beneficiaries.[3]

AREAS OF EMPHASIS

The LCRP recognizes that there is a broad range of unanswered research questions that are potentially critical to advancing prevention, detection, treatments, and cures for lung cancer. To meet this substantial need, the LCRP has identified Topic Areas for increased emphasis to address the needs of both the scientific and consumer communities. These Areas of Emphasis include prevention of lung cancer as well as prevention of recurrence and/or metastasis; screening and early detection; understanding how lung cancer starts, progresses, and what are non-tobacco contributors to lung cancer; improving strategies to treat, assist in therapeutic decision-making, and limit development of treatment resistance; and improving approaches to lung cancer care delivery.



FY09-FY20 LCRP Portfolio Investment by Areas of Emphasis

2020 Congressional Appropriations, Research Investment, and Withholds and Management Costs

Congressional Appropriations	Research Investment	Withholds and Management Costs
$14M	Career Development Award ..... $804,250 Clinical Translational Research Partnership Award ..... $3,755,997 Concept Award ..... $1,759,578 Idea Development Award ..... $3,469,190 Investigator Initiated Translational Research Award ..... $2,619,082 Modifications to ongoing awards $77,151	USAMRDC ..... $270,200 SBIR/STTR ..... $470,000 Mgt Costs (5.84%) $774,552
Total: $14M	**Total:** $12,485,248	**Total:** $1,514,752

[1] U.S. Secretary of Defense. 2016. Memorandum for secretaries of the military departments. Washington, DC: U.S. Secretary of Defense.

[2] Odani S, Agaku IT, Graffunder CM, et al. 2018. Tobacco product use among military veterans–United States, 2010-2015. *Morbidity and Mortality Weekly Report (MMWR)* 67:7-12. https://www.cdc.gov/mmwr/volumes/67/wr/mm6701a2.htm

[3] Data provided by the Armed Forces Health Surveillance Branch based on electronic records within the Defense Medical Surveillance System (DMSS).

"The DOD LCRP plays such an important role in accelerating research, specifically by funding many innovative early studies that have advanced and helped change the landscape of lung cancer research. There's still a lot of work to be done; I've witnessed all that we can accomplish when we work together alongside patient research advocates. I really appreciate the DOD recognizing that the patient perspective is important in every step of the process."
Jill Feldman, LUNGevity, FY20-FY21 Programmatic Panel Member

PROMISING RESEARCH ALONG THE CANCER CARE SPECTRUM

Area of Emphasis	Research Highlights
Biology/Etiology	
Molecular Mechanisms of Initiation and Progression	 **The Therapeutic Role of lncRNA-Mediated DNA Repair in Lung Cancer** ***Crystal Marconett, Ph.D., University of Southern California*** Previously, Dr. Marconett's team observed that loss of long non-coding RNA LINC00261 expression correlated to lung adenocarcinoma patients who were non-responders to immunotherapy due to loss of HLA-2 expression. With support from the LCRP, the team is further investigating the mechanisms by which LINC00261 affects DNA damage repair, tumorogenesis, and immune response in lung adenocarcinoma.
Prevention	
Prevention of Recurrence or Metastases	 **A Novel Peptide Suppresses Invasion and Metastasis in Rictor-Amplified Lung Cancer** ***Hsin-Sheng Yang, Ph.D., University of Kentucky*** Rictor, as part of the mTORC2 complex whose activity regulates cell proliferation and motility, is enhanced in some subtypes of lung cancer. Dr. Yang's research focuses on validating whether modulating Rictor activity via inhibition of mTORC2 with a novel peptide can suppress invasion and metastasis of Rictor-amplified lung cancer cells.
Detection, Diagnosis, Prognosis	
Screening and Early Detection	 **Biopsy Guidance of Lung Cancer Using a Novel Electromagnetic and Optical Coherence Tomography Platform** ***Melissa Suter, Ph.D., Massachusetts General Hospital*** Dr. Suter's team is developing and testing a lower-risk bronchoscopic biopsy guide and diagnostic tool using steerable electromagnetic optical coherence tomography technology. The team hopes to combine this technology with computed tomography (CT) screening to improve early detection and diagnosis by enhancing targeting and biopsy specimen collection accuracy of small lesions less invasively.
	  **Imaging and Exosomal Genomics as an Early Identifier of Lung Cancer** ***Utkan Demirci, Ph.D., Sandy Napel, Ph.D., Stanford University*** Drs. Demirci and Napel are collaboratively developing a platform that improves early detection and diagnostic accuracy. They are combining PET/CT imaging technology with exosomal genetic signature data to build a platform that can differentiate malignant from benign nodules.
Treatment	
Treatment	  **EMT Targeting Vaccination, Concurrent with Chemoimmunotherapy, in Advanced NSCLC** ***Laura Riolobos, Ph.D., Rafael Santana-Davila, M.D., University of Washington*** Drs. Riolobos and Santana-Davila developed a multi-antigen vaccine that targets the epithelial to mesenchymal transition pathway responsible for cancer cells that anchor to grow and metastasize. With LCRP funding support, the team is now collaboratively testing this vaccine in a phase 2 clinical trial, in combination with immune checkpoint inhibitor therapy, hoping to improve the efficacy of immunotherapy in advanced non-small cell lung cancer treatment (NSCLC) patients.
	  **Anti-PD1 in Combination with an Inhibitor of PCSK9 to Increase MHC Class I Molecule Expression on Tumor Cells as Immunotherapy for NSCLC** ***Scott Antonia, M.D., Ph.D., Chuan-Yuan Li, Ph.D., Duke University*** In a pilot clinical trial, Drs. Antonia and Li are evaluating the safety of combination immunotherapy anti-PD-1 nivolumab and anti-CTLA-4 ipilimumab with anti-PCSK9 evolocumab. This multi-faceted approach is aimed to restore T cell mediated elimination of tumor cells.

LUPUS RESEARCH PROGRAM

Vision: To cure lupus through partnership of scientists, clinicians, and consumers

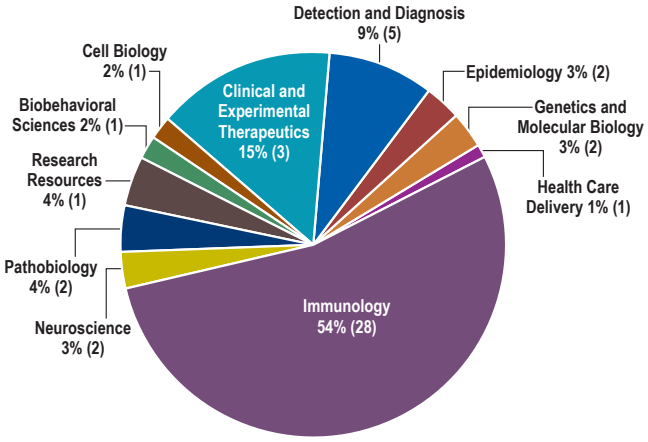
Mission: Fund research to understand, prevent, and diagnose lupus and to improve treatments and quality of life of patients, including Service Members, Veterans, and beneficiaries

PROGRAM HISTORY

Congress first funded lupus research as a Topic Area in the Peer Review Medical Research Program. From FY05-FY16, the CDMRP funded 21 lupus research awards for a total of $20.6M. In 2017 Congress initiated the Peer Reviewed Lupus Research Program (LRP) to provide support for innovative and impactful research of exceptional scientific merit that addresses significant issues and gaps in lupus research. Appropriations for the LRP from FY17 through FY20 totaled $25M. For FY21, the Defense Appropriations Act provides $10M to the LRP to support innovative and impactful research that addresses significant issues in lupus. Thus far, 48 awards have been funded through the LRP to support innovative, high-risk, high-reward studies, shifting current paradigms with the hope of improving treatments and quality of life for those living with lupus.

Lupus is a heterogeneous autoimmune disease that is difficult to diagnose and treat. There is currently no test available to diagnose lupus, and it may take months or years for a person to be correctly diagnosed. Because lupus attacks healthy cells and tissues in many parts of the body, patients can experience a wide range of symptoms such as fatigue, joint pain, skin lesions, and headaches.

Lupus can also cause inflammation in the kidneys, brain, blood vessels, lungs, and heart, which can result in serious complications, including organ damage. Treatment options for lupus are highly dependent on an individual patient's symptoms, meaning the patient may require a diverse team of healthcare specialists. Some of the most commonly used drugs to treat lupus include non-steroidal anti-inflammatory drugs, corticosteroids, and immunosuppressants; however, long-term use of these treatments can result in serious side effects, including kidney problems, stomach bleeding, liver damage, increased risk of infection, decreased fertility, and increased risk of cancer. Better treatment options are a critical need for lupus patients.



FY17-FY20 LRP Portfolio Investment by SCS Code
$22.1M, 48 Awards (Number of Awards)

"[LRP scientific peer review is] one of the best study sections that I attend. It is wonderful to hear patients' perspectives on proposals along with diverse experts' in the field."
Harris Perlman, Ph.D., Northwestern University Feinberg School of Medicine, FY17-FY20 Peer Reviewer

2020 Congressional Appropriations, Research Investment, and Withholds and Management Costs

Congressional Appropriations	Research Investment	Withholds and Management Costs
$10M	Idea Award ..... $299,937 Impact Award ..... $5,977,130 Transformative Vision Award ..... $2,499,992 Modifications to ongoing awards..... $77,308	USAMRDC ..... $193,300 SBIR/STTR .....$335,000 Mgt Costs (6.52%).... $617,333
Total: $10M	**Total:** $8,854,367	**Total:** $1,145,633

"The exciting inclusion of a consumer advocate to the Lupus Transformative Vision Award gives voice to the collective patient experience and the impact of treatment, shedding light on quality-of-life issues as defined by the patients themselves and leading to a better understanding of the feasibility of requirements for patient participation in future studies."
Cindy Coney, Lupus Foundation of America, FY17-FY21 Programmatic Panel Member

FY21 TRANSFORMATIVE VISION AWARD (TVA)

Applications are required to address the following Focus Area:

- Design and implement an intervention either at the individual and/or healthcare system level to improve the quality of life for individuals living with lupus.

TVA CONSUMER ADVOCATE

In FY21, the LRP is requiring inclusion of one or more consumer advocate(s) for TVA applications, who will be integral throughout the planning and implementation of the research project. The role of the consumer advocate is to provide objective input on the research and its potential impact for individuals with, or at risk for, lupus.

Correlation of Atmospheric Pollution with SLE Flare Activity

George Stojan, M.D., Johns Hopkins University

The Johns Hopkins University received FY18 funding from the CDMRP's LRP to pursue work on a proposal submitted by Dr. George Stojan. The project examined the association between environmental triggers and organ-specific disease flares in systemic lupus erythematosus (SLE), a condition with both genetic and environmental risk factors.

The project, a novel analysis of spatiotemporal clusters in the Hopkins Lupus Cohort, used data from the Environmental Protection Agency and the National Oceanic and Atmospheric Administration to identify environmental patterns associated with SLE disease flares. Dr. Stojan's research identified large-scale, multi-year spatiotemporal clusters of lupus organ-specific flares that did not conform to any previously described infectious or environmental clusters. The cluster patterns differed in extent and location for the various organ-specific flare types (i.e., rash, joint involvement, serositis, neurologic, pulmonary, renal, and hematologic). Most of the identified clusters (except serositis) changed in significance, temporal, or spatial extent after adjusting for environmental covariates, indicating that the clusters were at least partially driven by the environmental covariates. The outcomes of the study are important as an initial analysis of environmental effects on SLE disease activity and will be useful as a basis for future research to further clarify the role of environmental factors on SLE pathogenesis and heterogeneity, as well as potentially forming the basis for predictive models of lupus flares.[1]

Reference:

[1] Stojan G, Kvit A, Curriero FC, and Petri M. 2020. A spatiotemporal analysis of organ-specific lupus flares in relation to atmospheric variables and fine particulate matter pollution. *Arthritis & Rheumatology* 72(7):1134-1142. https://jhu.pure.elsevier.com/en/publications/a-spatiotemporal-analysis-of-organ-specific-lupus-flares-in-relat

Phara Policar, LRP Consumer Reviewer

"The Challenges I Have Encountered with Lupus Expanded My Ability To Be a Powerful Voice"

After living with symptoms such as low-grade fevers, skin rashes, debilitating fatigue, and joint pain for an extended period of time, Phara Policar was diagnosed with lupus in 1998, and for many years, she lived in denial while her health continued to deteriorate. She eventually found the Lupus Foundation of America (LFA), which aims to improve the quality of life for all people affected by lupus through research, education, support, and advocacy.

In FY18, she was nominated by the LFA to serve as a consumer reviewer on the LRP peer review panel. She felt a warm welcome among her fellow panel members as they worked toward the common goal of funding research to understand, prevent, and diagnose lupus and to improve treatments and quality of life of patients. Phara considers her participation on the LRP peer review panel a rewarding experience that has expanded her understanding of the progression and clinical manifestations of the disease. She feels that the CDMRP review process holds consumer perspectives in the highest regard, which ensures that the voices of the lupus patient community are heard and taken into account when making funding recommendations. Although the pipeline for advancing new therapies is often long and complicated, the addition of the consumer perspective allows the most needed solutions to be prioritized.

Phara says, "Not only have I regained control over the direction of my own life, but I also get to be an example of what is possible for others who are still navigating their way through this experience."

MELANOMA RESEARCH PROGRAM

Vision: Prevent melanoma initiation and progression

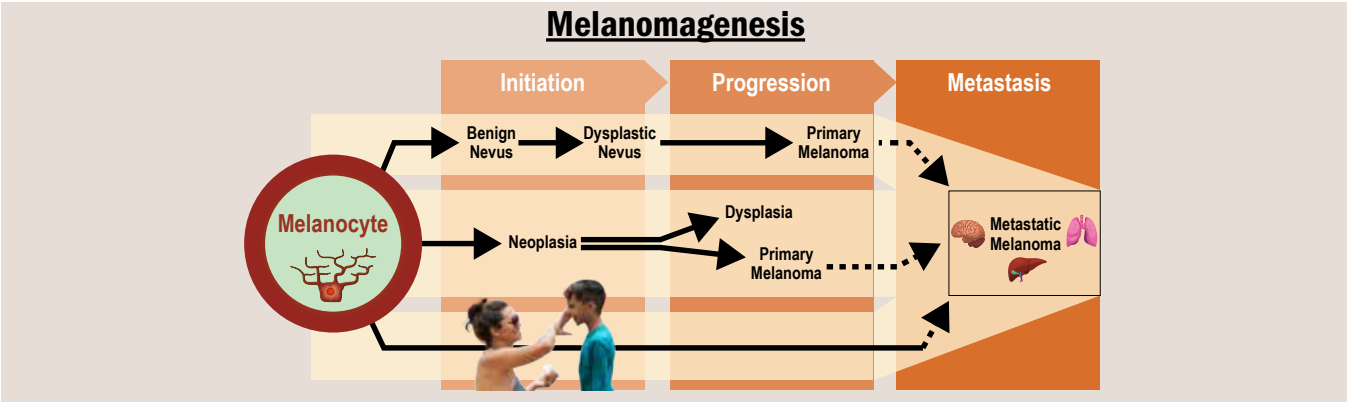
Mission: Promote earlier interventions to enhance mission readiness and diminish melanoma burden on Service Members, Veterans, and the American public

PROGRAM HISTORY

The vision of the Peer Reviewed Melanoma Research Program (MRP) is to prevent melanoma initiation and progression. In 2020, the United States experienced an estimated 100,350 new cases of melanoma; a 9% increase in new cases since 2018. Melanoma diagnoses are increasing among active-duty Service Members, with the greatest incidence rates in the Air Force, Navy, and Marines. To address the need to prevent the development of this deadly disease and increase earlier intervention strategies, the MRP commits to enhancing U.S. military personnel mission readiness and to diminishing the disease burden of melanoma on Service Members, Veterans, and the American public.

FY21 MRP CHALLENGE STATEMENT

MRP challenges the research community to redefine the concept of prevention to include the entire melanomagenesis process. In recognizing that melanomagenesis is a multi-step process, a new paradigm of prevention may include detection, monitoring, and impeding the initiation and progression of primary melanoma, blocking emergence from tumor dormancy, and inihibiting the development of micro-metastases. Each step along the disease process from initiation to metastasis is an opportunity to stop progression. The MRP looks to shift the paradigm of prevention of all types of melanoma by investing in research studies focused on eliminating the development and progression of cutaneous or rare melanoma variants.



"The CDMRP is a central player in our efforts to eradicate melanoma, the most devastating form of skin cancer. The program's focus on melanoma prevention, either before it occurs or prior to metastasis, offers a long-sought opportunity to address a clinically unmet need. I am confident that efforts advanced through this research initiative will lead to better strategies to prevent, monitor, and treat melanoma to benefit patient health."

Ze'ev Ronai, Ph.D., Sanford Burnham Prebys Medical Discovery Institute, FY21-FY22 Programmatic Panel Chair

2020 Congressional Appropriations, Research Investment, and Withholds and Management Costs

Congressional Appropriations	Research Investment	Withholds and Management Costs
$20M	Idea Award ..... $6,084,736 Mid-Career Accelerator Award ..... $4,463,622 Team Science Award ..... $3,626,698 Translational Research Award ..... $3,684,892 Modifications to ongoing awards..... $126,000	USAMRDC ..... $386,580 SBIR/STTR ..... $671,000 Mgt Costs (5.08%).... $956,472
Total: $20M	**Total:** $17,985,948	**Total:** $2,014,052

TYPES OF MELANOMA

Cutaneous | Acral | Pediatric | Ocular | Mucosal | Leptomeningeal

FY21 MRP FOCUS AREAS

Emerging Gaps in Melanoma

- Identify methods to decrease risk of melanoma development beyond sunscreen and protective clothing.
- Identify and understand risk factor determinants for melanoma, including variants.
- Develop prediction and surveillance tools for distinguishing patients at risk for recurrence and/or metastasis. Identify biological determinants to differentiate patient populations.
- Identify how the tumor microenvironment impacts tumor initiation, response to therapy, progression, and dormancy.
- Understand how precursor lesions and endogenous host factors may lead to melanomagenesis.
- Understand mechanisms that underlie metastatic spread to different (regional/nodal) sites or the different distant sites of metastasis from acral, mucosal, and uveal melanomas.
- Delineate the molecular pathways, tumor microenvironment, immune responses that influence metastatic spread, recurrence, and/or dormancy.
- Develop new decision-making tools for the detection and diagnosis of melanoma that include easily accessible technology (beyond the dermoscope) for primary care physicians and dermatologists.

The Role of the Tumor Microbiome in Mucosal Melanoma Development and Antitumor Immunity
Kasey Couts, Ph.D., University of Colorado at Denver
Idea Award

Mucosal melanoma is a rare subtype of melanoma that arises from melanocytes located in mucosa tissues. It remains poorly understood, with very few effective treatments. The goal of this project is to investigate the role of microbiome dysbiosis in mucosal melanoma epigenetic silencing, innate immune pathogen sensing genes, anti-tumor immunity, and immune checkpoint blockade resistance. Antibiotic and epigenetic-modifying drugs will be evaluated for their ability to restore anti-tumor immunity and anti-PD1 sensitivity in mucosal melanoma microbiome-altered mouse models.

Germline Genetic Determinants of Transformation of Uveal Nevi to Melanoma: Towards Early Diagnosis and Prevention of Disease Progression
Mohamed Abdel-Rahman, Ph.D., The Ohio State University
Mid-Career Accelerator Award

Uveal melanoma is the most common primary eye cancer. Most cases of uveal melanoma develop from preexisting nevi in the eye, but may go undiagnosed during routine eye exams. The objective of this proposal is to expand understanding of the genetics of uveal melanoma susceptibility, which could facilitate identification of uveal nevi that are at high risk for malignant transformation.

Establishing the Role of Deployments in Melanoma in the Military
Jennifer Powers, M.D., University of Iowa
Rudolph Rull, Ph.D., M.P.H., Naval Health Research Center
Gregory Gray, M.D., M.P.H., Duke University
Team Science Award

The deployment of 2 million U.S. Service Members to Iraq and Afghanistan led to exposures of higher ultraviolet radiation than what is typically experienced in the U.S. Between 2005-2014, melanoma was the most common cancer diagnosis among Service Members. This project will leverage data collected from the Millennium Cohort Study to investigate the hypothesis that Service Members deployed to more equatorial latitudes during the Persian Gulf War (1990-1991) and/or Operation Enduring Freedom/Operation Iraqi Freedom/Operation New Dawn (OEF/OIF/OND) Cohort (2001-2016) as well as other deployed groups will have experienced higher incidence of sunburn, melanoma, and other sun-related entities.

MILITARY BURN RESEARCH PROGRAM

Vision: Deliver the best burn trauma care to improve health and performance outcomes in support of the Warfighter

Mission: Identify and address gaps in burn trauma care through military-focused translational research

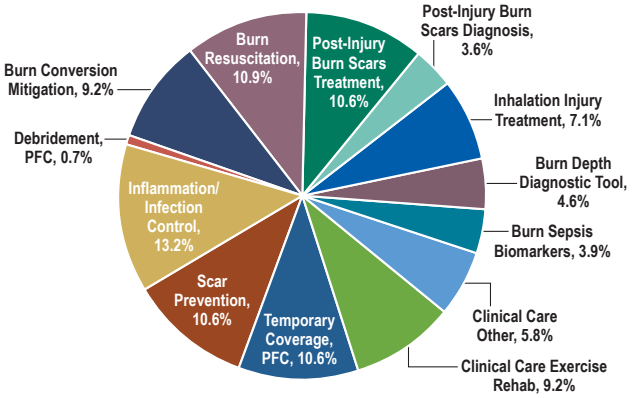
PROGRAM HISTORY

According to the American Burn Association, nearly 500,000 patients in the United States require treatment for burn injuries annually. Approximately 40,000 of those patients require acute inpatient care, and 3,000 patients succumb to their burn injuries.[1-2] The mean total healthcare cost per burn patient in high-income countries has been estimated at $88,218 (range $704-$717,306).

Burns sustained during combat or combat training are often more severe, and complicated by other traumatic injuries, than burns occurring in the civilian setting. Historically, burns comprise some 5%-20% of all wounds sustained in post-World War II conflicts. The Defense Medical Epidemiology Database reported nearly 130,000 ambulatory visits with a primary burn-injury diagnosis code among active component Service Members from 2006-2018. The majority of combat-associated burns result from explosive device detonation, leading to a greater Injury Severity Score, an increase in inhalation injuries, and a larger, full-thickness burn size. Treatment of burn casualties can be rather complex, as burns sustained during combat or combat training often occur simultaneously with other severe traumatic injuries.

In addition to the more obvious treatment to the burn site, care must also be provided to support the patient throughout the continuum of care for all sustained trauma as well as any physiological and psychosocial factors that may delay healing or return to duty.

The 2011 initiation of the Peer Reviewed Military Burn Research Program (MBRP) was intended to address combat-related and trauma-induced burn injuries, as well as to improve health and performance outcomes for Service Members, Veterans, and the general public. Since FY11, $80M has been appropriated to the program by Congress. Through FY20, MBRP has funded 55 research projects that have provided key research insights in advancing therapies for burn-injured patients and impacting standard practice.



FY11-FY21 MBRP Portfolio Investment by Focus Area (% Based on Dollars Invested per Focus Area)

"In future conflicts we cannot assume uniform air superiority or electromagnetic dominance. Small units distributed across a large battle space may not be kept under the umbrella of constant communication and casualty evacuation coverage we enjoy today. MBRP seeks out and funds research efforts to ensure our warfighters deploy with simple and reliable tools to protect thermal injuries and minimize burn wound conversion in prolonged field care settings."

Lt Col Bryan Forney (U.S. Marines, retired), Wounded Warrior Battalion, FY17-FY21 Programmatic Panel Member

2020 Congressional Appropriations, Research Investment, and Withholds and Management Costs

Congressional Appropriations	Research Investment	Withholds and Management Costs
$10M	Clinical Translational Research Award ..... $8,544,318 Modifications to ongoing awards..... $688,025	USAMRDC ..... $200,000 Mgt Costs (5.79%) $567,657
Total: $10M	**Total:** $9,232,343	**Total:** $767,657

[1] Delaplain PT and Joe VC. 2018. Problems and costs that could be addressed by improved burn and wound care training in health professions education. *AMA J Ethics*. 20(6):560-566. https://journalofethics.ama-assn.org/article/problems-and-costs-could-be-addressed-improved-burn-and-wound-care-training-health-professions/2018-06

[2] American Burn Association. Burn incidence fact sheet. http://ameriburn.org/who-we-are/media/burn-incidence- fact-sheet/. Accessed March 27, 2019.

"A recent article in Foreign Policy stated that we are 100% right 0% of the time. Hence, we have to cast a wide net and plan for any potential blindspots we may have in the foreseeable future. This year's MBRP Focus Areas reflect this."

COL Kevin Chung (U.S. Army), M.D., Uniformed Services University of the Health Sciences, FY15-FY21 Programmatic Panel Co-Chair

ADVANCES IN FIELD-CAPABLE MBRP RESEARCH EFFORTS

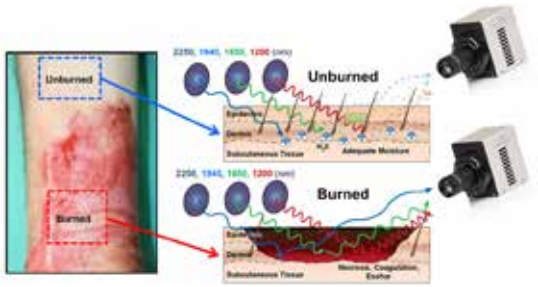
Current burn care in the prehospital field environment is limited to temporary coverage of burn wounds with dressings while simultaneously stabilizing and arranging for immediate evacuation of the severely burned patient to a burn care-capable hospital setting. This is true during both civilian mass casualty events such as the 2013 Boston Marathon bombing and during combat and military field training environments. In addition, delayed evacuation further complicates burn wound treatment, potentially leading to deeper burn wounds, reduced intravascular fluid volume, infections, sepsis, or death. The following MBRP-funded products under development aim to provide earlier burn care in the early acute phase, prior to arrival at a burn center, to reduce the progression of inflammation and other cellular assaults.

Temporary Coverage for Acute Burns

Split-thickness skin grafts remain the gold standard treatment for severe burns within the hospital environment; unfortunately, this type of treatment is untenable in a prehospital environment or in the prolonged care field environment of the combat zone. While waiting for definitive burn treatment, temporary wound coverage is employed by the combat medic, using standard dressings that can be easily carried in a first aid bag. A clear need exists for wound coverage solutions that both protect the burn wound and allow the healing process to begin. Cadaver skin or other cellular skin substitutes typically used in the burn center hospital environment require specialized storage and hardware requirements that may not be conducive to the prolonged care field environment. Alternative, viable options currently exist, such as the fish skin-derived product under development by Dr. Hilmar Kjartansson. Kerecis Omega3 GraftGuide is an FDA-cleared medical device indicated for wound healing and is currently under development through the MBRP for deep-partial to full-thickness burn indication. Using minimal processing techniques, this unique fish skin product provides an intact 3D structure to initiate wound healing and carries no risk of disease transmission from fish to humans. The product is stable at room temperature (picture on left) and can be meshed using standard clinical mesher to expand coverage (picture on right). Images show an adult burn patient with burns to both lower limbs, one covered with Kerecis fish skin and the other covered with human cadaver skin. Both products are meshed and applied to debrided burn wounds. Outcomes after 90 days post-burn demonstrate healed skin; note the mesh-like appearance after cadaver skin treatment is more pronounced than the fish skin treated burn. The results of this study will answer the call for effective anti-inflammatory strategies and high-quality tissue-engineered skin replacements for full-thickness burn injuries.

Portable Burn Wound Assessment

The short-wave assessment tool (SWAT) aims to address capability gaps in the ability to objectively assess burn wound depth and predict burn wound healing outcomes, thereby helping to guide burn care, including treatment and debridement. The SWAT consists of a portable handheld camera-based system with a built-in light source that measures the amount of light absorbed and/or reflected from the wound. The camera picks up the amount of absorbed and/or reflected light in the short-wave infrared region at several discrete wavelengths. The software algorithm then correlates the spectral readings to the water and structural composition of the burn wound to produce an image that informs the care provider on the burn depth, including identification of areas and depths of non-viable tissues for debridement. Further SWAT development will incorporate real-time streaming of burn images with a superimposed outline of debridement boundaries on a computer monitor and on the burn skin itself to guide more precise debridement. The PIs for this effort are Drs. Benjamin Levi and Caroline Park at the University of Texas Southwestern.



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MULTIPLE SCLEROSIS RESEARCH PROGRAM

Vision: To prevent, cure, reverse, or slow the progression, and lessen the personal and societal impact of multiple sclerosis

Mission: To support pioneering concepts and high-impact research relevant to the prevention, etiology, pathogenesis, assessment, treatment, and ultimate cure of multiple sclerosis for the benefit of Service Members, Veterans, and the American public

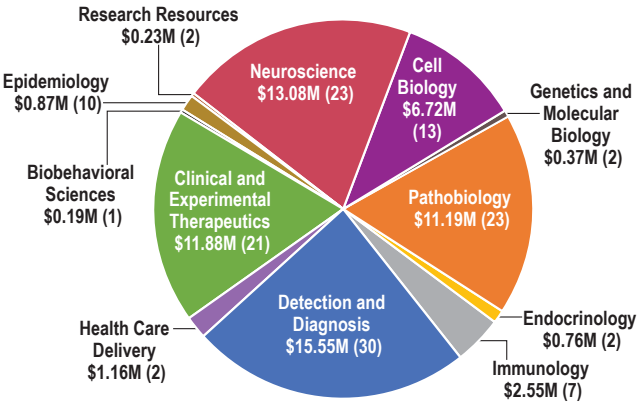
PROGRAM HISTORY

In FY09, $5M in congressional appropriations established the Peer Reviewed Multiple Sclerosis Research Program (MSRP) to fund meritorious research related to multiple sclerosis (MS). It has been funded continuously since, receiving a cumulative total of $93.1M in appropriations. The overall goal of the program has been to lessen the personal and societal impact of multiple sclerosis by identifying approaches to prevent, cure, or slow the progress of the disease. With these appropriations, the program has built a broad research portfolio of 131 awards that include mechanistic studies to understand the underlying causes of the disease initiation, progression, and symptoms; studies to detect and measure disease progression; and small pilot clinical trials to identify approaches to manage the many symptoms of the disease.

MS is a chronic immune-mediated disease that causes damage to the CNS and affects nearly 1 million individuals in the United States. It has a higher incidence in U.S. Armed Forces personnel than in the general population. MS is characterized by the demyelination of axons due to the immune system incorrectly attacking healthy tissues in the CNS. Symptoms of MS vary widely in type and severity and may include pain, fatigue, depression, anxiety, loss of bladder control, impaired mobility, and cognitive, motor, visual, or sexual dysfunction. Currently, there is no cure for MS.

FOCUS AREAS

- CNS regenerative potential in demyelinating conditions
- Correlates of disease activity and progression in MS
- Biology and measurement of MS symptoms
- Factors contributing to MS etiology, prodrome, onset, and disease course
- Interactions between MS and COVID-19



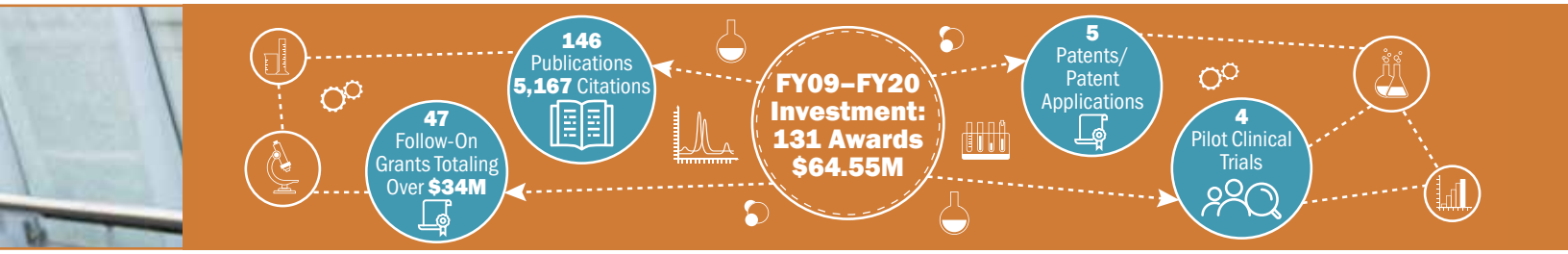
FY09-FY20 MSRP Portfolio Investment by SCS Code (Numbers of Awards)

"I had the honor of participating in the MSRP review process in 2020 and I'm very happy that Paralyzed Veterans of America nominated me. I gained great insight into the efforts that are underway to find solutions to a disorder that has a huge impact on me and others. The MSRP review process gave me a better understanding of my own MS."

Ismal "Izzy" Abass, Paralyzed Veterans of America, FY20 Consumer Peer Reviewer

2020 Congressional Appropriations, Research Investment, and Withholds and Management Costs

Congressional Appropriations	Research Investment	Withholds and Management Costs
$16M	Clinical Trial Award ..... $4,303,115 Exploration – Hypothesis Development Award – Established Investigator ..... $591,377 Exploration – Hypothesis Development Award – New Investigator ..... $1,189,082 Investigator-Initiated Research Award $8,649,091	USAMRDC ..... $309,260 SBIR/STTR ..... $537,000 Mgt Costs (2.78%) $421,075
Total: $16M	**Total:** $14,732,665	**Total:** $1,267,335



RESEARCH OUTCOMES AND HIGHLIGHTS

MSRP-funded research projects have resulted in numerous impactful outcomes, including high-impact publications, knowledge- and data-sharing at scientific and patient-focused conferences, follow-up research grants from other federal and non-federal funding agencies to further expand their MSRP-funded studies, and patents/patent applications. The MSRP-funded pilot clinical trials aim to improve cognition, reduce fatigue, or increase mobility in people with MS, to enhance their quality of life.

Exploring Remyelination in MS: Myelin, Metformin, and Mitochondria

Holly Colognato, Ph.D., State University of New York, Stony Brook

Dr. Colognato aimed to understand the inner workings of myelin-forming cells in order to design and produce successful myelin repair therapies. They first sought to determine AMP-activated protein kinase (AMPK) loss-of-function and impact on myelin repair in a cuprizone MS mouse model of demyelination using an FDA-approved AMPK activator, metformin, and observed that metformin treatment enhanced myelin levels in the corpus callosum. Specifically, metformin increased myelin protein mRNA levels at 24 hours, which resulted in increased myelin-related protein-positive cells and resulted in changes in oligodendrocyte morphology and mitochondrial respiration. Additionally, low doses of metformin resulted in increased oxygen consumption rates (OCR) and an increased rate of glycolysis in oligodendrocytes, while higher doses suppressed OCR. Overall, these findings may lead to future studies to translate these findings into clinical trials and further drug discovery to help repair myelin in MS patients.

Exercise Training, Metabolic Changes, and Symptoms in People with MS

Pavan Bhargava, M.D., Johns Hopkins University

Dr. Bhargava studied the metabolic changes from exercise in people with MS (pwMS). Utilizing metabolomics, they studied alterations in the metabolome and the relationship to changes in MS-related symptoms and collected data on hip strength, walking, fatigue, and physical activity. In MS participants, the program led to increases in hip strength, walking, increased walking speed, reduced fatigue, and increased overall activity. They also identified 51 metabolites that changed in pwMS following the intervention, while there was no significant change in the metabolome in healthy controls. They specifically observed a significant relationship between sex steroid (dehydroepiandrosterone sulfate) metabolism changes and fatigue scores as well as a relationship between fatty acid metabolism and cardiovascular fitness (maximum rate of oxygen consumption) in pwMS. Identification of metabolic pathways associated with symptomatic benefits could lead to the development of alternative treatment strategies, both pharmacologic and neurorehabilitative, for targeting these pathways.

Imaging Measures Reflect Cognitive Changes Over Time in Multiple Sclerosis Patients

Katherine A. Koenig, Ph.D., The Cleveland Clinic

Dr. Koenig sought to develop a brain imaging measure to track or predict cognitive decline in MS patients. This study assessed 80 participants with MS at baseline, a 1-year interval, and a third time point. They found that healthier white matter at baseline related to stable cognitive performance over time and a decline in white matter health was more likely to score lower on cognitive tests at follow-up. They also observed that changes in connectivity of the prefrontal cortex related to changes in verbal episodic memory, and functional connectivity was unable to significantly differentiate which participants were cognitively stable or declining. Finally, total volumes of both the left and right hippocampus were related to changes in performance on visual spatial episodic memory. These findings could serve as clinical predictors of cognitive decline in MS. Future work will focus on refinement, automation of methods, and validation on a larger scale to confirm the use of these measures as a tool to track cognitive changes and decline in MS populations.

NEUROFIBROMATOSIS RESEARCH PROGRAM

Vision: Decrease the clinical impact of neurofibromatosis

Mission: Promote research directed toward the understanding, diagnosis, and treatment of NF1, NF2, and schwannomatosis to enhance the quality of life for persons with these disorders that impact Service Members, Veterans, and the general public

PROGRAM HISTORY

An appropriation of $8M established the Peer Reviewed Neurofibromatosis Research Program (NFRP) in FY96. From then through FY20, $362.85M has been appropriated to the program for research of NF1, NF2, and schwannomatosis. The appropriation for FY21 is $20M. The NFRP has invested in key initiatives to support the development of critical resources, sponsor multidisciplinary collaborations, bring talented investigators into the field, and promote the translation of promising ideas into the clinic. The program's research portfolio includes 451 awards.

MILITARY RELEVANCE

The underlying causes of neurofibromatosis (NF) have a direct relationship to tumor formation in many non-cancer sarcomas and malignant cancers, requiring extensive treatment and inpatient services. From 2009 to 2018, there were 2,469 new cases of NF within the MHS; 44% of these cases were predominately family members of active and reserve component Service Members.[1] In addition, from 2009 to 2018 there were 6,609 DOD beneficiaries who had outpatient or inpatient encounters, totaling 15,389 hospital bed days.[1] NFRP-supported research is paving the way to finding treatments for individuals with NF that impact military Service Members, Veterans, and their beneficiaries.

AREAS OF EMPHASIS

Each year, the NFRP Programmatic Panel members identify and recommend important research, and these are highlighted as Areas of Emphasis in the program announcements. The FY21 NFRP strongly encourages research applications that specifically address one or more of the following:

- Biomarker discovery, utility, development, and validation
- Non-tumor manifestations including but not limited to: pain, cognitive manifestations, sleep
- Heterogeneity of NF-related tumors
- Novel disease and treatment response markers using genetics, genomics, epigenetics, systems biology, metabolomics, or similar approaches
- Preclinical efficacy studies
- Target identification, drug discovery
- Nutritional, environmental, and other modifiers of NF
- Health services research

"I first heard about NFRP in 2019 when I was nominated by NF Michigan. The review process gave me a chance to learn more about the amazing research that is being done to advance care for those with NF. I enjoyed hearing from scientists and clinicians regarding the proposal reviews in order to better understand their aims, and I could tell my consumer input was valued. The consumer advocate community does so much to advance the quality of life of those living with various conditions. I look forward to being involved with the CDMRP in the future!"

Mikaela Bradley, Neurofibromatosis Michigan, FY20 Consumer Peer Reviewer

2020 Congressional Appropriations, Research Investment, and Withholds and Management Costs

Congressional Appropriations	Research Investment	Withholds and Management Costs
$15.0M	Clinical Trial Award ..... $1,181,297 Early Investigator Research Award ..... $292,000 Exploration - Hypothesis Development Award ..... $839,337 Investigator - Initiated Research Award ..... $5,534,449 New Investigator Award..... $3,413,920 Synergistic Idea Award ..... $2,226,595 Modifications to ongoing awards..... $462,000	USAMRDC ..... $300,000 Mgt Costs (5.1%) $750,402
Total: $15.0M	**Total:** $13,949,598	**Total:** $1,050,402

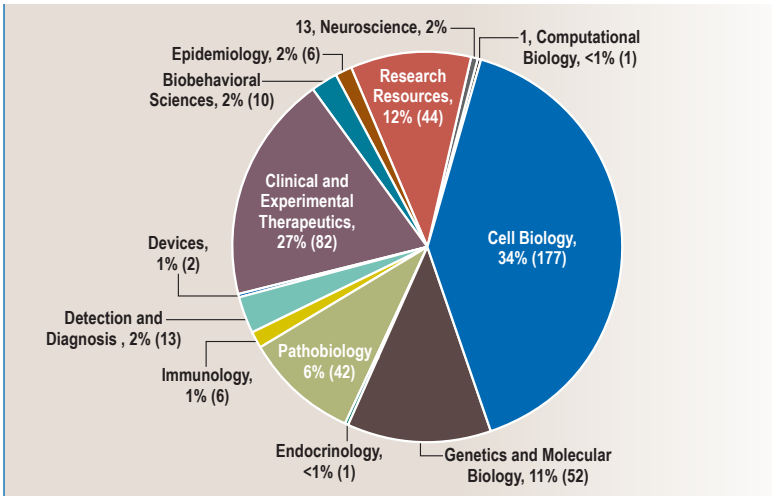
[1] Data provided by the Armed Forces Health Surveillance Branch based on electronic records within DMSS. Does not include care received outside the MHS.

"My 18-year-old son lives with neurofibromatosis type 2. His journey thus far has not been an easy one. I am very proud to be a part of the peer review system that assists in fielding new and innovative neurofibromatosis research for funding. The NFRP process gives me such hope for new treatments. I hope to continue participating, in any way I can, to further awareness, treatments, and one day, a cure for this disorder."

Tammy Benson-O'Brien, Texas Neurofibromatosis Foundation, FY17, FY19, FY20 Consumer Peer Reviewer

THE NEUROFIBROMATOSIS CLINICAL TRIALS CONSORTIUM

The NFRP initiated the Neurofibromatosis Clinical Trials Consortium (NFCTC) in FY05 to develop and perform phase 1 and 2 clinical trials for the management and treatment of NF complications in children and adults. The NFCTC currently consists of 15 primary sites and has 10 additional affiliate sites. Dr. Bruce Korf at the University of Alabama at Birmingham is the Operations Center Director, and Dr. Michael Fisher at the Children's Hospital of Philadelphia/University of Pennsylvania leads the NFCTC Steering Committee. Since FY05, the NFCTC has been supported by additional awards from the NFRP in FY06, FY11, and FY16.



NFRP FY96-FY20 Portfolio Investment by SCS Code

RESEARCH HIGHLIGHTS


Dr. Bruce Korf


Dr. Michael Fisher


Dr. Wade Clapp

Cabozantinib for Neurofibromatosis Type 1-Related Plexiform Neurofibromas: A Phase 2 Trial

Patients with neurofibromatosis type 1 (NF1)-related plexiform neurofibroma (PN) tend to experience pain, functional limitations, disfigurement, and threat to life. Radiation and chemotherapy have not been found to be very effective, and surgery is typically not feasible due to proximity to vital organs. While Selumetinib has benefited some patients, additional treatment options are needed. Based on the success of Cabozantinib in preclinical models in the laboratory of consortium member, Dr. Wade Clapp, the NFCTC, led by Drs. Bruce Korf and Michael Fisher, began a phase 2, multicenter clinical trial of Cabozantinib (given by mouth) in NF1 patients aged 16 years and older with progressive and/or inoperable PN. Results indicate that there is clinical activity against PN through reduction in tumor volume in over 40% of the participants. Safety analyses show good tolerability and rare, serious side effects. Based on these results, the trial expanded to include younger participants, ages 3-15 years, to further establish drug efficacy and safety.

Everolimus Therapy for NF1-Optic Gliomas in Children: A Clinical Trial

Nicole Ullrich, M.D., Ph.D., Boston Children's Hospital

Children with NF1 are at risk to develop low-grade gliomas (LGGs). When LGGs occur along the optic pathway, this can result in decreased visual acuity. Traditional chemotherapy has been used to treat NF1-LGGs; however, targeted treatment has not been well-studied in the NF population. One potential target is the mammalian target of rapamycin (mTOR), which is implicated in LGG development. Based on preclinical data, a clinical trial was launched as part of the NFCTC, led by Dr. Nicole Ullrich and team, to investigate the efficacy of the oral mTOR inhibitor, everolimus, given daily in children with NF1-associated LGGs who had previously undergone chemotherapy treatment. Shrinkage or arrest of tumor growth was noted in 68% of participants; of these, 10/15 remained free of progression after treatment. A retrospective analysis of the impact of everolimus on visual function revealed stable visual acuity in the majority of children with optic pathway gliomas (76%) and an improvement in vision in a smaller group (16%). Given the well-tolerated toxicity profile and stabilization of visual function, everolimus is an effective treatment option for children with NF1-associated LGGs.

NEUROTOXIN EXPOSURE TREATMENT PARKINSON'S

Vision: To eliminate Parkinson's disease through neurotoxin exposure and treatment-related research in partnership with scientists and consumers

Mission: Support Parkinson's research investigating the underlying biologic mechanisms and therapeutic interventions of neurodegenerative effects caused by deployment, environmental, and occupational exposures in Service Members and Veterans

PROGRAM HISTORY

Congress initiated the Peer Reviewed Neurotoxin Exposure Treatment Parkinson's (NETP) program in FY97 to provide support for Parkinson's research investigating the underlying biologic mechanisms and therapeutic interventions of neurodegenerative effects caused by deployment, environmental, and occupational exposures.

Research into military Service-related risk factors is critical for past, present, and future Service Members who may be affected by Parkinson's disease (PD).

The congressional appropriations for the NETP from FY97 through FY20 totaled $468.75M. The FY21 appropriation is $16M.

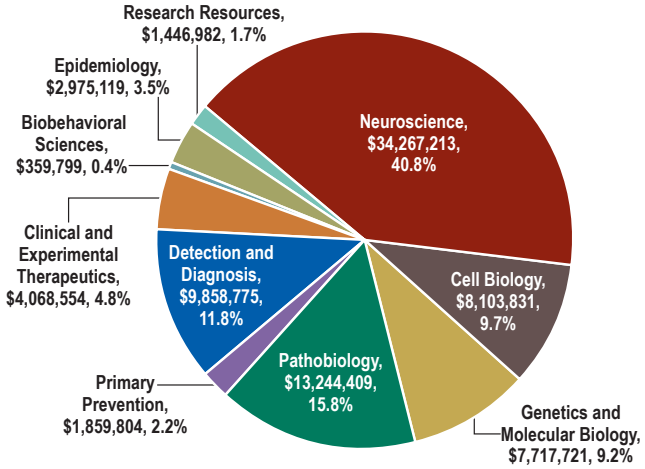
NETP STRATEGIC GOALS

The long-term NETP Program Strategic Goals within the context of the program's mission are:

- Determine the biologic mechanisms of neurodegeneration in PD.
- Delineate how deployment, environmental, and occupational exposures in combination with gene-environment interactions impact the development and progression of PD.
- Understand the mechanisms of the cognitive, psychiatric, and other non-motor symptoms of PD.
- Determine how circuitry and synaptic mechanisms of PD, dopamine refractory motor symptoms, and treatment-associated dystonia influence PD progression.
- Identify the biological mechanisms of impact from exercise and other lifestyle modifications on neurodegeneration in PD.

Within the context of the NETP mission and long-term strategic goals, the following are the NETP Focus Areas:

- Basic biology and clinical implications of non-motor symptoms that could lead to the development of new treatments for PD.
- Environmental exposures and gene-environment interactions at prodromal or clinically diagnosed PD.
- Circuitry and synaptic mechanisms of PD, dopamine refractory motor symptoms, and treatment-associated dystonia that could lead to development of new treatments in patients.
- Understand disease heterogeneity to enable precision medicine approaches to PD treatments.



FY15-FY20 NETP Portfolio Investment

2020 Congressional Appropriations, Research Investment, and Withholds and Management Costs

Congressional Appropriations	Research Investment	Withholds and Management Costs
$16M	Early Investigator Research Award ..... $1,199,228 Investigator-Initiated Research Award ..... $7,354,706 Synergistic Idea Award $5,990,039	USAMRDC ..... $320,000 Mgt Costs (7.25%) . $1,136,027
Total: $16M	**Total:** $14,543,973	**Total:** $1,456,027

Shari Bridge, Consumer Advocate, *NETP Programmatic Panel*

I served in the Army Reserves from 1982 to 1996. I served as a medic/ambulance driver in the 477th Medical Company based in Duluth, Minnesota. My unit was deployed to the Middle East for Operation Desert Storm. We were based out of Saudi Arabia, but as ambulance drivers we were given many temporary assignments at field hospital units all over the region.

I first noticed symptoms in about 2011. It started out as dystonia in my right foot as I was running. Initially, I didn't notice it until about 10 miles into a run (oh, how I miss being able to do that!). I was diagnosed with compartment syndrome and had a nerve release, which had no effect. Eventually, I started having other symptoms as well. My reflexes were slowing, and even simple movements were becoming increasingly difficult. I've always described it as feeling as if I was always underwater, having to push against some force that wasn't there. My fine motor skills started to deteriorate, and I developed the Parkinson's mask – the loss of expression in my face. I would look in the mirror and just saw this blank face staring back at me. I would force myself to smile. Eventually, after about 6 years of these symptoms, I saw the doctor who finally diagnosed PD. She put me on medication that almost immediately made a huge impact. I could move again without it being a struggle!

I formed a team for the Parkinson's Foundation Moving Day, which led to my becoming a research advocate for the foundation. That, in turn, led to my becoming a consumer advocate on the NETP Programmatic Panel, allowing me to provide feedback on research grant applications directly related to PD. As a non-scientific person (I am a social worker by education), this has been such a great opportunity, and I feel incredibly blessed to have it. Working with this panel, I have the chance to see what is happening now in PD research. To be able to listen to and interact with such knowledgeable experts in the field has been a great honor. The goal, of course, is to get closer to a cure. One mile at a time is the running-themed mantra I always use.

The Environmental Effects of Nicotine on Risk for Parkinson's Disease

Abby Lauren Olsen, M.D., Ph.D., Brigham and Women's Faulkner Hospital

Many genes and environmental factors are known to influence the risk of developing PD, but the contribution of each and how they interact is unknown. Through an award to the Brigham and Women's Hospital, Dr. Abby Olsen investigated the previously identified gene-environment interaction between the gene *SV2C* and smoking.[1] Smoking has been inversely associated with PD in many epidemiologic studies, but results of clinical trials testing nicotine (the presumed active ingredient in tobacco) as a therapy for PD have been mixed, perhaps in part due to genetic variation.

To understand how the *SV2C* gene relates to smoking, Dr. Olsen developed a unique model of Parkinsonism[2-4] in the fruit fly, Drosophila melanogaster. She identified the Drosophila genes that are similar to the human *SV2C* genes (orthologs) and treated the fruit flies with nicotine. She found that nicotine treatment can rescue motor dysfunction and neurodegeneration caused by alpha-synuclein in Drosophila, and that this rescue depends on normal *SV2C* levels. When *SV2C* is knocked down, nicotine not only fails to improve neurodegeneration but, in fact, results in even fewer dopaminergic neurons and worse motor functioning than with alpha-synuclein alone. The result provides a good confirmation of the gene-environment interaction between nicotine and the *SV2C* gene as well as identifying a potential alpha-synuclein mechanistic association.

The fruit fly work is being paired with human studies to identify novel gene-environment interactions in the Harvard Biomarkers Study Parkinson's disease cohort. Despite added challenges due to the COVID pandemic, this research has already identified a possible novel association between asthma and PD as well as confirmed links to head trauma and smoking,[5] and future work will investigate genetic variation in combination with these environmental factors.

[1] Hill-Burns EM, Singh N, Ganguly P, et al. 2013. A genetic basis for the variable effect of smoking/nicotine on Parkinson's disease. *Pharmacogenomics J.*13(6):530-537. https://www.nature.com/articles/tpj201238

[2] Ordonez DG, Lee MK and Feany MB. 2018. α-synuclein induces mitochondrial dysfunction through spectrin and the actin cytoskeleton. *Neuron. 97:108-124.e6.* https://pubmed.ncbi.nlm.nih.gov/29249285/

[3] Olsen AL and Feany MB. 2019. Glial alpha-synuclein promotes neurodegeneration characterized by a distinct transcriptional program in vivo. *Glia.* 67(10):1933-1957. https://pubmed.ncbi.nlm.nih.gov/31267577/

[4] Olsen AL and Feany MB. 2021. Parkinson's disease risk genes act in glia to control neuronal α-synuclein toxicity. *Neurobio Disease*. 105482. https://www.sciencedirect.com/science/article/pii/S096999612100231X

[5] Olsen AL, Locascio JJ, and Scherzer CR. 2021. Defining the Parkinson's disease health-ome. In preparation.

ORTHOTICS AND PROSTHETICS OUTCOMES RESEARCH PROGRAM

Vision: The highest possible quality of life for our injured Service Members and beneficiaries through the advancement of knowledge in orthotics- and prosthetics-related research

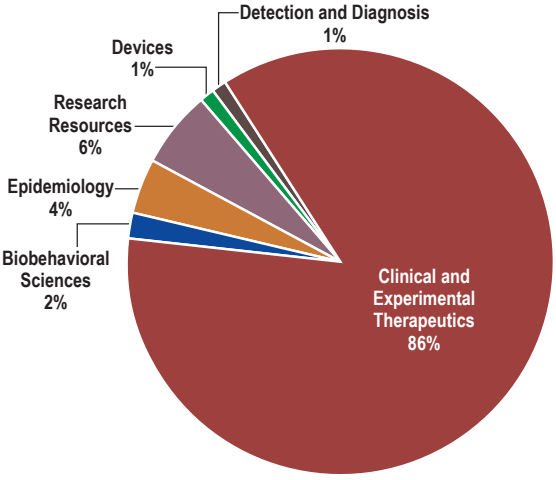
Mission: Advance orthotic and prosthetic research to optimize evidence-based care and clinical outcomes for military-related neuromusculoskeletal injury

PROGRAM HISTORY

Since the Orthotics and Prosthetics Outcomes Research Program (OPORP)'s inception in FY14, through FY20, Congress has directed appropriations totaling $75M to OPORP to support research of exceptional scientific merit with the potential to make a significant impact on improving the health and well-being of Service Members, Veterans, and other individuals living with and recovering from traumatic neuromusculoskeletal injury. This includes research to evaluate the comparative effectiveness and functional outcomes associated with prosthetic and orthotic clinical interventions as well as improving the ability to carry out daily activities, enhancing work productivity, and increasing the possibility of returning to work/duty.

FOCUS AREAS

The FY20 OPORP Focus Areas reflect program goals to optimize patient outcomes through advances that impact orthoses or prostheses form, fit, and function. Awards funded that address Orthoses or Prostheses Form will optimize patient outcomes through the analysis and characterization of variables related to the form of currently available clinical options such as device size, shape, material, and/or configurations. Projects addressing Orthoses or Prostheses Fit optimize patient outcomes related to human-device interface through the analysis of variables in currently available clinical options that facilitate fit-related metrics such as comfort and/or usability. Projects addressing Orthoses or Prostheses Function optimize patient outcomes through the analysis of variables related to currently available device function, such as device control, sensors, and passive or active response with respect to activities of daily living and other real-world activities.



FY14-FY20 OPORP Investments $68,030,838 in 70 awards

"It is incredible to see some of the projects that are being put forth for funding in this program, and the realization that my input means something to these research teams. I'm grateful that I'm able to provide my insights to the program in hopes that it can go on to benefit and assist others in my situation."

Evan Reichenthal, Oscar Mike Foundation, FY20-FY21 Consumer Peer Reviewer

2020 Congressional Appropriations, Research Investment, and Withholds and Management Costs

Congressional Appropriations	Research Investment	Withholds and Management Costs
$15M	Clinical Research Award - Funding Level 1, Funding Level 2 .....$2,872,252 Clinical Trial Award - Funding Level 1, Funding Level 2.....$10,569,427	USAMRDC .....$289,940 SBIR/STTR .....$503,000 Mgt Costs (5.39%).... $765,381
Total: $15M	**Total:** $13,441,679	**Total:** $1,558,321

OPORP strives to improve our understanding and ultimately advance the implementation of the most effective prescriptions for prosthetic and orthotic devices, treatment, and rehabilitation, and prevention of secondary health effects.

RELEVANCE TO MILITARY HEALTH

An estimated 26,000 Service Members suffered a traumatic extremity injury from deployments (as of October 2015) during OIF/OEF/OND.[1] For those who served in OIF/OEF, the mean lifetime prosthetic and assistive device costs for unilateral upper-limb, unilateral lower-limb, bilateral upper-limb, and multiple limb loss groups are approximately $823,000, $1.46M, $2.16M, and $2.90M, respectively.[2] Additionally, an estimated 40,000 Veterans are served by the VA Prosthetics and Sensory Aids Services. In 2016, Medicare approved payment for nearly 3.04 million orthotic codes that accounted for more than $1B in Medicare expenditures and allowed nearly 2.11 million prosthetic services for over $717M in expenditures.[3]

RESEARCH OUTCOMES

Andrew Sawers, Ph.D., C.P.O., University of Illinois at Chicago (shown left)
Brian Hafner, Ph.D., University of Washington (shown right)

Dr. Andrew Sawers and his co-investigator, Dr. Brian Hafner, evaluated the psychometric properties of a novel Narrow Beam Walking Test (NBWT) for assessing fall risk in lower limb prosthesis (LLP) users. Their research to date demonstrates that the NBWT discriminates fallers and non-fallers with greater accuracy than existing clinical balance tests. The NBWT procedures were designed to accommodate practice run effects, unlike previously available tests, which increases diagnostic accuracy, and the proposed validity indices would allow clinicians to assign a probability of falling to an individual LLP user rather than a simple faller or non-faller designation. The team also developed and tested a fall-type classification framework to better understand the circumstances surrounding falls.

Brent Winslow, Ph.D., Design Interactive, Inc.

Traditional myoelectric prostheses require intensive training to effectively operate. Dr. Brent Winslow's team developed the Enhanced Auto-Diagnostic Adaptive Precision Training for Myoelectric Prosthesis users (eADAPT-MP) system, which uses a wireless muscle-sensing band, a series of mobile games, and a web-based provider portal to improve myoelectric training. The technology is expected to improve device compliance and skill, translating into better clinical and psychosocial outcomes for Veteran amputees, including return to work/duty, employment, and increased quality of life. The eADAPT-MP system also allows for telerehabilitation, which reduces the burden of travel on the patient, while increasing provider efficiency via enhanced data availability.

FY20 RESEARCH PROJECT SPOTLIGHT

A Wearable Sensing System for Continuous Assessment of Outcomes of Orthotic Hand Users in Real World Settings

Xiaogang Hu, Ph.D., The University of North Carolina at Chapel Hill

Recovery of hand function is the most challenging rehabilitation following a stroke or TBI. With the support of an FY20 OPORP Clinical Research Award, Dr. Hu is optimizing a wearable sensing system to capture real-time outcome measures of hand impairment and its impact to daily function by combining continuous monitoring of hand utility with clinical assessments and user objective feedback. The sensing system and correlated assessments can facilitate adaptive and personalized orthoses prescription, maximize the benefits of orthoses functions, and transform the current standard of care to restore hand functions in Service Members and Veterans with impaired hand function.

[1] Rábago CA, Clouser M, Dearth CL, et al. 2016. The extremity trauma and amputation center of excellence: Overview of the research and surveillance division. *Military Medicine* 181(11/12):3. https://academic.oup.com/milmed/article/181/suppl_4/3/4209444

[2] Blough DK, Hubbard S, McFarland LV, et al. 2010. Prosthetic cost projections for Service Members with major limb loss from Vietnam and OIF/OEF. *Journal of Rehabilitation Research & Development.* 47(4):387-402. https://pubmed.ncbi.nlm.nih.gov/20803406/

[3] American Orthotic and Prosthetic Association (AOPA) Fact Sheet: https://aopanet.org/media/fact-sheet/.

OVARIAN CANCER RESEARCH PROGRAM

Vision: To eliminate ovarian cancer

Mission: To support patient-centered research to prevent, detect, treat, and cure ovarian cancer to enhance the health and well-being of Service Members, Veterans, retirees, their family members, and all women impacted by this disease

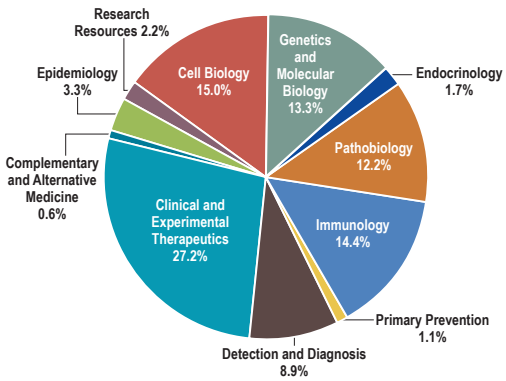
PROGRAM HISTORY

Congress established the Ovarian Cancer Research Program (OCRP) in 1997 to define and address the critical research gaps facing the ovarian cancer community. The OCRP has defined a strategic plan that highlights the high-impact research goals critical to achieving its vision and mission. From FY97-FY21, the OCRP has received $406.5M in congressional appropriations and is the second-leading funder of ovarian cancer research in the U.S. Through FY20, the OCRP has funded 526 research awards, resulting in over 1,956 peer-reviewed publications and 122 patent applications. The appropriation for OCRP for FY21 is $35M.

The success of the OCRP can be attributed to the synergistic efforts of many dedicated individuals. One hallmark of the OCRP is the partnership of survivor advocates with scientists and clinicians to set program priorities, design funding opportunities, evaluate research applications, and identify high-impact, innovative research that will make important contributions to the field and patient/survivor care. Survivors provide their unique perspectives on the human dimension of this disease to support research that reflects their community's concerns. They are also an integral part of many research projects supported by the OCRP.

PROGRAM PORTFOLIO

The OCRP is transforming the landscape of ovarian cancer to the benefit of patients worldwide by funding high-impact research across the spectrum of care. To accomplish this, the OCRP invests in etiology, prevention, detection, diagnosis, survivorship, and quality-of-life issues, with the largest investment in therapeutics. The OCRP strategy targets the most critical needs along the research development pipeline, from basic to translational to clinical research and clinical trials, to push the field forward to our vision to "eliminate ovarian cancer."



FY15-FY20 Portfolio Investment by SCS Code

PROGRAM RELEVANCE TO MILITARY HEALTH

This program exists because approximately 22,240 women in the United States were diagnosed with ovarian cancer, and an estimated 14,070 were expected to die from the disease in 2018.[1] Approximately 11,800 female Service Members and wives and adult daughters of active-duty military will be diagnosed with ovarian cancer over the course of their lifetimes. The cost of ovarian cancer to our military is great, not only in terms of troop readiness, but also in terms of cancer care costs; treating these cases of ovarian cancer over these patients' lifetimes could cost TRICARE an estimated $971.2M.[2]

2020 Congressional Appropriations, Research Investment, and Withholds and Management Costs

Congressional Appropriations	Research Investment	Withholds and Management Costs
$35M	Clinical Translational Research Award ..... $3,834,702 Investigator-Initiated Research Award ..... $12,912,180 Ovarian Cancer Academy Award – Early-Career Investigator Award ..... $4,416,284 Pilot Award ..... $6,109,636 Proteogenomics Research Award ..... $620,953 Teal Expansion Award $3,269,760	USAMRDC ..... $676,520 SBIR/STTR ..... $1,174,000 Mgt Costs (5.99%) $1,985,965
Total: $35M	**Total:** $31,163,515	**Total:** $3,836,485

[1] The lifetime risk of a woman developing ovarian cancer is 1.2% according to NCI Cancer Stat Facts (http://seer.cancer.gov/statfacts/html/ovary.html).

[2] The average cost of frontline ovarian cancer therapy is $82,324, per the NIH (http://costprojections.cancer.gov/annual.costs.html).

"Being part of the review process allows us, survivors, to give input in what we believe would be life-changing for the people facing ovarian cancer. There is a deep level of gratitude and appreciation by the OCRP toward the consumer advocate community."

Ilana Feuchter, National Ovarian Cancer Coalition, FY18-FY19, FY21 Consumer Peer Reviewer

HIGH-IMPACT RESEARCH SUPPORTED BY THE OCRP

Prevention

- Precise risk assessment with mutations in non-BRCA genes
- Salpingectomy as a less invasive surgery option
- An algorithm to diagnose precursor lesions

Treatment

- The BROCA test, which predicts a better response to chemotherapy and improved overall survival
- Junctional openers to increase the efficacy of chemotherapy for recurrent ovarian cancer
- Exercise to reduce the effects of chemo-induced memory problems and cognitive dysfunction
- Accelerated FDA approval for rucaparib treatment in patients with prior chemotherapies and recurrences

Detection

- OVA1, an FDA-approved blood test that can better identify patients at high risk for malignant ovarian cancer
- Falloposcope system to identify ovarian cancer
- RAD51D, a genetic testing kit for women with ovarian cancer with or without breast cancer
- Identification of a mutator signature specific for homologous recombination deficiency

Survivorship

- Impact of daily self-administered relaxing acupuncture on fatigue, sleep, and quality of life in persistently fatigued ovarian cancer survivors
- Initiated two consortia focused on long-term survivorship

Bispecific Antibody Leads to Possible Therapeutic in High-Grade Serous Ovarian Cancer
Sarah J. Hill M.D., Ph.D., Dana-Farber Cancer Institute

High-grade serous ovarian cancer (HGSC) has limited early detection and therapeutic options. Because of this, HGSC has a lethality rate of approximately 70%, making it the most fatal form of ovarian cancer. Dr. Sarah Hill has used funding from an FY18 Pilot Award to examine a new therapeutic option for those with HGSC. Dr. Hill's research uses HGSC human tissue to grow 3D tumor spheres called organoids in culture, either alone or in co-culture with matched immune cells from the same tumor to understand how defects in DNA damage repair in the tumor cells may contribute to both targeted and immune therapy response. Dr. Hill's preliminary data showed that the organoids and co-cultures were accurate representations of the parent tumors, and that most HGSC organoids were unable to repair replication-associated DNA damage successfully. To better study why the tumors were unable to repair this type of damage and if targeting this defect might also synergize with the anti-tumor immune response, the Hill lab utilized funding from her DOD OCRP Pilot Award to understand the importance of fork instability, uncover mechanisms leading to DNA fork instability, and determine how these defects lead to therapeutic sensitivities, including immuno-oncologic agents, which can uncover more effective therapies against HGSC. Dr. Hill and her team published their findings about one of these possible new immune therapies in Cancer Research.

In the study, researchers conducted immune functional and single-cell RNA sequencing transcriptional profiling on HGSC organoid/immune cell co-cultures and treated them with a bispecific antibody (anti-programmed cell death protein 1/programmed death-ligand 1). When they compared this antibody across different types of immune cell types, they identified immune checkpoint blockage (ICB) targets that current HGSC therapies have missed. The bispecific antibody induced changes in both T- and natural killer (NK) cells. The NK cells went from an inactive to a more active state and exhibited cytotoxic phenotypes, suggesting it could be a possible missing component of the current ICB-induced immune response in HGSC. A subset of T-cells also transitioned to become more active with the bispecific antibody. In addition, the bispecific antibody induced downregulation of the bromodomain-containing protein, BRD1. These results demonstrate that changes in NK and subsets of T-cells could be keys to inducing effective immune responses; therefore, immune therapies, like BRD1 inhibitors, may have increased efficacy in HGSC.

PANCREATIC CANCER RESEARCH PROGRAM

Vision: Reduce the burden of pancreatic cancer among Service Members, Veterans, their families, and the American public

Mission: Promote rigorous, innovative, high-impact research that leads to earlier pancreatic cancer diagnosis and new therapeutic tools through collaboration

PROGRAM HISTORY

Pancreatic cancer is an aggressive disease that is difficult to detect. There is no screening test available to identify the disease, and because there may be no symptoms present, it is often diagnosed at an advanced stage, after the cancer has spread to other organs in the body. Standard treatment avenues for cancer, such as chemotherapy and radiation, have limited effectiveness in pancreatic cancer patients.

Based on current Surveillance, Epidemiology, and End Results (SEER) data from the NCI, there were an estimated 60,430 new cases of pancreatic cancer diagnosed in the U.S. in 2021 thus far. 48,220 deaths have also been attributed to pancreatic cancer so far this year. Pancreatic cancer is also the eleventh most common type of cancer in the United States, representing 3.2% of all new cancer diagnoses every year. The 5-year survival rate for those with pancreatic cancer is 10.8%.

For FY20, Congress established the Peer Reviewed Pancreatic Cancer Research Program (PCARP) with an appropriation of $6M. With this new program, PCARP will invest in research focusing on advancing our understanding of pancreatic cancer for the benefit of Service Members, Veterans, their families, and the American public. During the FY20 cycle, five projects were funded that address at least one of the FY20 PCARP Focus Areas.

FOCUS AREAS & STRATEGIC PLAN

The PCARP developed a multifaceted strategic direction based upon the current state of pancreatic cancer research and the needs of the pancreatic cancer community. The PCARP will (1) fill gaps and advance knowledge that will drive new and innovative clinical trials for pancreatic cancer, (2) expand pancreatic cancer expertise by bridging diverse scientific fields, (3) facilitate a multidisciplinary approach to advancing scientific knowledge of pancreatic cancer, and (4) recruit and retain young investigators dedicated to pancreatic cancer research.

In order to fulfill its strategic direction, the PCARP created seven Focus Areas, which include:

- Early detection research for pancreatic cancer, including studies of individuals with pre-diabetes and diabetes and/or those in underserved ethnic and minority communities
- Supportive care and patient-reported outcomes, quality of life, and perspectives during treatment and survivorship
- Understanding the relationship between metabolic disruptions in pancreatic cancer and their systemic effects, including diabetes and cachexia
- Understanding precursors, origins, and early progression of pancreatic cancer
- Understanding the events that promote pancreatic cancer metastasis
- Understanding the relationship between oncogenic signaling and the tumor microenvironment that drives drug resistance and therapeutic response
- New drug development targeted toward cancer sensitivity and resistance mechanisms, including immune mechanisms of resistance

2020 Congressional Appropriations, Research Investment, and Withholds and Management Costs

Congressional Appropriations	Research Investment	Withholds and Management Costs
$6M	Idea Development Award ..... $2,820,191 Translational Research Partnership Award $2,228,266	USAMRDC ..... $115,980 SBIR/STTR ..... $201,000 Mgt Costs (11.17%)...$634,563
Total: $6M	**Total:** $5,048,457	**Total:** $951,543

"As the first federal research program completely dedicated to pancreatic cancer, the ability to evaluate research priorities each year provides timely support for gap-filling, innovative projects with significant potential to improve and extend the lives of patients. Scientists and patient advocates working side-by-side on the yearly evaluations only strengthens the potential for high impact advances!"

Lynn Matrisian, Ph.D., Pancreatic Cancer Action Network, FY20-FY21 Programmatic Panel Member

FY20 PCARP FUNDED AWARDS

Award Mechanism	Research Highlights
	Focus Area: **Understanding the relationship between oncogenic signaling and the tumor microenvironment that drives drug resistance and therapeutic response**
Translational Research Partnership Award - Pilot Clinical Trial	  **Modulating Neural Signaling in the Treatment of Pancreatic Cancer** ***Timothy Wang, Ph.D., Columbia University Medical Center*** ***Susan Bates, M.D., Columbia University Medical Center*** This study will help understand how the nerves and cells surrounding tumors effect growth and metastasis. Using normal and tumor organoids established from patient samples, the PIs will examine the effects of nerve signaling on immune response and conduct a phase 2 trial using a cholinergic agent to stimulate the nervous system in combination with two established pancreatic cancer therapeutics, gemcitabine and nab-paclitaxel.
	Focus Area: **New drug development targeted toward cancer sensitivity and resistance mechanisms, including immune mechanisms of resistance**
Idea Development Award - Partnering PI Option	  **Targeting KRAS-Dysregulated Metabolism for Novel Therapeutic Approaches** ***Channing Der, Ph.D., University of North Carolina, Chapel Hill*** ***Kirsten Bryant, Ph.D., University of North Carolina, Chapel Hill*** The study team will screen metabolism-related genes and identify new metabolic targets to combine with ERK inhibitors or autophagy inhibitors to treat KRAS-mutant pancreatic ductal adenocarcinoma. The investigators will investigate the contribution of the tumor microenvironment to metabolism-based, combination-inhibitor treatment strategies and attempt to identify combination treatment approaches for future clinical trial evaluation.
	Focus Area: **Development of pharmacological, immunological, or genetic interception approaches**
Idea Development Award - Partnering PI Option	  **Targeting Hepatocyte-Derived Factors to Improve the Efficacy of Immunotherapy in Pancreatic Cancer** ***Gregory Beatty, M.D., Ph.D., University of Pennsylvania*** ***Meredith Stone, Ph.D., University of Pennsylvania*** This study aims to determine if the liver can serve as a therapeutic target to improve immunotherapy in pancreatic ductal adenocarcinoma patients. The team will define mechanisms by which the liver regulates immunosurveillance in pancreatic cancer and develop potential therapeutics to intervene on liver-directed immune dysfunction.
Idea Development Award	 **Manipulating Myeloid Cells to Promote Immunotherapy Efficacy of Pancreatic Ductal Adenocarcinoma** ***Ingunn Stromnes, M.D., Ph.D., University of Minnesota, Twin Cities*** This project will investigate differentiation of monocytes in pancreatic cancer and whether manipulating differentiation can increase the efficacy of immune-based therapies. A candidate gene approach will be used to determine if it is possible to increase the efficacy of immunotherapies by interfering with the suppressive program in myeloid cells by specific gene targeting.
	Focus Area: **Integration of biologic and imaging biomarkers to drive more precise and earlier detection and prognosis**
Translational Research Partnership Award	  **Integrating Radiomics and Genomics to Improve the Clinical Assessment of Pancreatic Cysts and Early Detection of Pancreatic Cancer** ***Randall Brand, M.D., University of Pittsburgh*** ***Eugene Koay, M.D., Ph.D., MD Anderson Cancer Center*** This partnership award aims to identify a comprehensive set of radiomic and genomic biomarkers to improve the diagnostic and prognostic accuracy of detecting mucinous cysts and predicting their progression to high-grade dysplasia and early-stage pancreatic ductal adenocarcinoma. Such an advance could improve survival and reduce overtreatment by accurately categorizing patients who require less intensive surveillance from those who will benefit from early surgical intervention and intensified surveillance protocols.

PEER REVIEWED ALZHEIMER'S RESEARCH PROGRAM

Vision: To address the long-term implications of military Service as they pertain to Alzheimer's disease and Alzheimer's disease-related dementias

Mission: Devoted to (1) understanding the association between military Service-related risk factors and Alzheimer's disease/Alzheimer's disease-related dementias, and (2) reducing the burden on affected individuals and caregivers, especially in the military and Veteran communities

PROGRAM HISTORY

Military personnel may face an increased risk for developing Alzheimer's disease (AD) or a related dementia as they age.[1] Risk factors such as TBI, vascular disease, lifestyle, and alterations in cognition or behavior may affect military personnel at higher rates or with greater severity than the general public. These risk factors may be linked to early dementia symptoms such as aggression, memory loss, depression, and symptoms similar to those of other neurological diseases, long before a dementia diagnosis can be established by a medical professional.

The Peer Reviewed Alzheimer's Research Program (PRARP) was initiated in FY11 and since then, the program has addressed the long-term consequences of TBI as they pertain to AD and AD-related dementias (ADRD). In FY21, the program is expanding its focus to include the spectrum of military health risk factors that may lead to AD and ADRD. The program emphasizes not only basic research related to understanding and diagnosing the molecular basis of dementia after military Service, but also tools and strategies that can improve the quality of life of individuals living with AD or ADRD by their implementation in care settings.

OVERARCHING CHALLENGES AND MILITARY RISK FACTORS

Consistent with the PRARP's mission and vision, the program faces six overarching challenges for FY21. These overarching challenges represent long-standing research goals for the program. The PRARP recognizes the needs for foundational research, clinical studies, improved diagnostics and prognostics, and epidemiological studies. Together, these four elements will increase our understanding of the association between military Service-related risk factors and AD/ADRD. The PRARP also recognizes that advances in quality-of-life interventions, as well as improvements in family and care support are needed to improve dementia care. By funding research in these two spaces, the PRARP seeks out research that will reduce the burden of dementia on individuals living with dementia and their caregivers.

The PRARP has come to recognize eight military risk factors that may increase symptoms of AD/ADRD, such as memory or behavioral impairments. The PRARP has funded research into both TBI and neuropsychological/neurobehavioral risk factors since its inception. The PRARP has also come to recognize the roles of additional risk factors that may be modifiable or related to the biology of aging (e.g., vascular, inflammatory, genetic, metabolic, or sleep-related). It is unknown how these risk factors work independently or in concert with each other to lead to the onset of Alzheimer's disease or a related dementia.

2020 Congressional Appropriations, Research Investment, and Withholds and Management Costs

Congressional Appropriations	Research Investment	Withholds and Management Costs
$15M	Accelerating Diagnostics for Traumatic Brain Injury Research Award ..... $2,798,011 Convergence Science Research Award..... $3,301,020 Innovations in Care and Support Award..... $750,113 Leveraging Approaches for Innovation in Care and Support Award.....$5,355,478 Research Partnership Award..... $1,295,595 Modifications to ongoing awards.....$146,272	USAMRDC .....$289,940 SBIR/STTR .....$503,000 Mgt Costs (3.95%) $560,571
Total: $15M	**Total:** $13,646,489	**Total:** $1,353,511

[1] Snyder HM, Carare RO, DeKosky ST, et al. 2018. Military-related risk factors for dementia. *Alzheimers Dement* 14(12):1651-1662. doi:10.1016/j.jalz.2018.08.011. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6281800/

"While the PRARP focuses on finding novel strategies that can help us understand how to reduce or eliminate the effects of TBI, Alzheimer's, and other related dementias, we also look for methods to reduce the level of caregiver stress and burden. We have recognized and identified this area as a potential area of research and inquiry. The Alzheimer's Association is proud to collaborate with the PRARP."

Lucien Richardson, Alzheimer's Association, FY17-FY21 Programmatic Panel Member

Innovations in Device Design May Lead to New Treatments for TBI and Dementia

Pierre Mourad, Ph.D., University of Washington

Dementia has several sources, with a range of signs and symptoms. These complexities have kept researchers and clinicians from effectively treating dementia. One clear sign of dementia based upon direct analysis of brain tissue is the deposition of aberrant proteins within the brain – amyloid beta plaque between neurons and, likely causally, then tau within neurons. Studies show that TBI is a likely risk factor for the subsequent develop of dementia, including Alzheimer's disease, with injury increasing the accumulation of aberrant proteins in the brain. Strategies to reduce or remove plaque and tau are at the forefront of clinical science for dementia. Dr. Pierre D. Mourad of the University of Washington is testing a novel device to remove these errant proteins. The technique uses ultrasound to cause cells in the brain (microglia) to digest the plaque, thereby reducing plaque itself; hence, possibly reducing or eliminating subsequent tau deposition. His group has shown nearly 50% reduction in plaque after only 5 days of hour-long treatment of a mouse model of Alzheimer's disease. Dr Mourad's group is at the early stage of testing this approach using mouse models that combine Alzheimer's disease and moderate TBI. One advantage of Dr. Mourad's approach is that it involves no systemic delivery of medication (hence no systemic side effects), simply transcranial application of ultrasound that targets desired portions of brain with large-scale results after just a few applications.

"Recent literature, including my own, suggests that near-diagnostic ultrasound can dilate blood vessels and cause microglia to remove amyloid beta plaque from the brains of mouse models of disease. If we can do this in humans after TBI we may have the ability to reduce the likelihood or severity of their subsequent dementia, for which they are at greater risk than if they did not experience traumatic brain injury."

Dr. Pierre Mourad

Bringing Researchers, Clinicians and Communities Together Through Consortia

Denise Krch, Ph.D., Kessler Foundation

Effective dementia care management is a challenge, since dementia symptoms can vary between persons. Memory and behavioral symptoms are often accompanied by symptoms such as depression. Many previous studies on care management were small and hard to reproduce. As a result, there is limited information about what to do to cope with the daily challenges of early- and late-stage dementia. One strategy is to organize researchers to systematically study how to improve care. In 2020, the PRARP offered the Leveraging Approaches for Innovation in Care and Support Award to support harmonized research in care management. The first consortia began their work in September 2021. One project, led Dr. Denise Krch of the Kessler Foundation, works with researchers at Franciscan Health and the University of Michigan to evaluate the Wellness, Coping, and Adaptation for Neurologic Conditions (WeCAN) intervention. WeCAN teaches self-management skills for coping, stress management, and problem solving to individuals living with cognitive impairments. Dr. Krch and colleagues will investigate two cohorts living with either TBI or dementia for this study. The unique focus of this study is on teaching both the person living with the neurological condition and their caregiver skills to improve interpersonal interactions, reduce stress, manage difficult emotions, and effectively problem-solve. If successful, this could be an important tool for clinicians to use in a healthcare setting to improve patient and caregiver quality of life and improve care management.

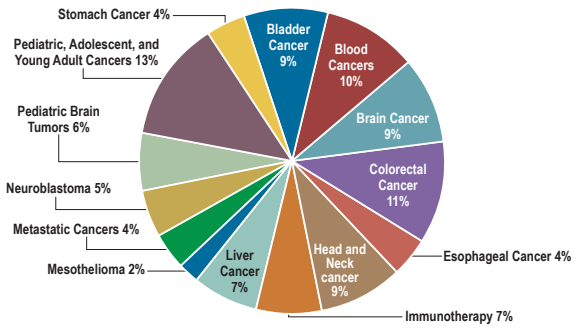
"When someone suffers a neurologic condition, their caregiver is affected as well. This means that not only do the patient and caregiver face burdens together, but they importantly have the opportunity to improve management of the condition as a team. This is the basis of the WeCAN treatment."

Dr. Denise Krch

PEER REVIEWED CANCER RESEARCH PROGRAM

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, Veterans, and the American public

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



FY20 PRCRP Portfolio Investment by Topc Area (% Dollars)

PROGRAM HISTORY

Since its inception in FY09, Congress designates the Topic Areas (specific cancers or research disciplines) to be funded under the Peer Reviewed Cancer Research Program (PRCRP) and that the research is relevant to Service Members and their families. In FY20, PRCRP established the first Convergent Science Virtual Cancer Center (CSVCC) focused on training Scholars in a cross-disciplinary method to catalyze faster career growth, foster awareness of cancer and military health concerns, and support advances in congressionally directed cancers.

PRCRP developed Overarching Challenges (see below) to address multiple issues in cancer research over the spectrum of different cancer topics in areas of critical gaps in cancer research, care, and/or patient outcomes to advance mission readiness of U.S. military members affected by cancer and improve quality of life by decreasing the burden of cancer on Service Members, their families, Veterans, and the American public.

SUMMARY OF OVERARCHING CHALLENGES*

- Identify/understand novel features driving cancer to improve outcomes for all ages.
- Identify/understand mechanisms behind cancer epigenetics, biological development, etiology, and genetic basis.
- Develop strategies and biomarkers to predict cancer risk, treatment resistance, recurrence, and advanced disease to mitigate risk.
- Develop and improve minimally invasive methods to detect cancer initiation, recurrence, and progression.
- Transform cancer treatment through the identification of novel biomarkers and new targets, especially for advanced disease, improve immunotherapy, and eliminate therapy toxicity risks.
- Develop strategies to improve ease of care/accessibility and to address survivorship issues.
- Improve prevention strategies, diagnosis, treatment, and outcomes for patients in underserved or under-recognized populations.
- Develop open access platform(s) or methods to coordinate and integrate multiple databases, biorepositories, and data sharing interfaces.

* https://cdmrp.army.mil/prcrp/default

2020 Congressional Appropriations, Research Investment, and Withholds and Management Costs

Congressional Appropriations	Research Investment by Topic Area		Withholds and Management Costs
$110M	Bladder Cancer.....$8,423,391 Blood Cancers..... $9,982,909 Brain Cancer.....$9,182,464 Colorectal Cancer..... $10,633,234 Esophageal Cancer.....$4,311,951 Head and Neck Cancer .....$8,858,543 Immunotherapy ..... $6,359,546 Liver Cancer.....$6,753,957	Mesothelioma ..... $2,148,614 Metastatic Cancers ..... $3,496,809 Neuroblastoma.....$4,773,088 Pediatric Brain Tumors..... $6,120,864 Pediatric, Adolescent, and Young Adult Cancers..... $12,286,688 Stomach Cancer.....$3,816,818 Modifications to ongoing awards $260,388	USAMRDC .....$2,126,200 SBIR/STTR .....$3,690,000 Mgt Costs (6.5%) ... $6,774,536
Total: $110M		**Total:** $97,409,264	**Total:** $12,590,736

Military Health Focus Areas

- ***Environmental exposure risk factors associated with cancer***
- ***Mission readiness, including knowledge gaps in cancer prevention, early detection/diagnosis, prognosis, treatment, and quality of life and/or survivorship***

CONVERGENT SCIENCE VIRTUAL CANCER CENTER

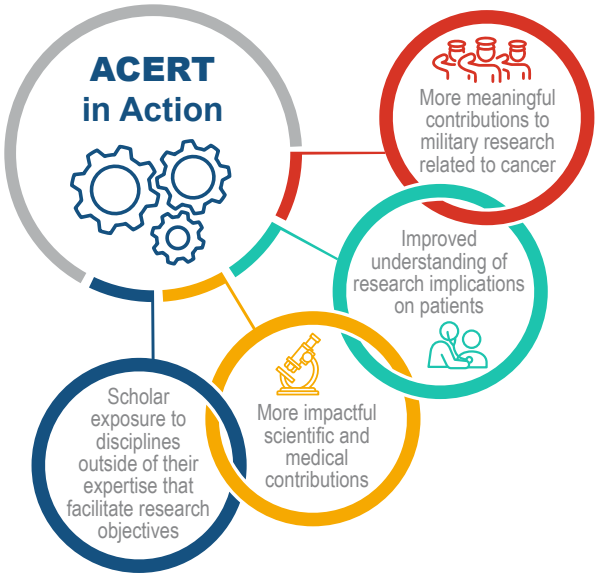
For FY20, PRCRP invested in the Virtual Cancer Center (VCC) Director Award and the Career Development Award - Scholar Option to establish the CSVCC. The focus of the groundbreaking CSVCC is to catalyze the training of early career independent investigators (Scholars) in convergent science. Drs. Dan Theodorescu (Cedars Sinai Cancer Center) and Peter Kuhn (University of Southern California) serve as the Director and Deputy Director respectively, of the CSVCC to lead the next generation of Scholars in a collegial, highly dynamic, and cutting-edge cancer center. Total FY20 investment of the PRCRP in this initiative (VCC plus Scholars) is $12.6M.

Dan Theodorescu M.D. Ph.D.
Cedars Sinai Cancer Center
CSVCC Director

Peter Kuhn Ph.D.
University of Southern California
CSVCC Deputy Director

Vision: Starting with early career cancer research Scholars, transform the fundamental cancer research culture into one that has the skills, awareness, and networks to collaboratively leverage the power of convergent science.

Mission: Use Adaptive Catalysis of ConvErgent Research Training (ACERT) to catalyze training of Scholars in convergent science through bespoke mentorship, workshops, and networking on a global scale with experts in different disciplines and varieties of cancers with the goal of making major improvements in patient outcomes in the FY20 PRCRP Topic Areas



Scholars

Abby M. Green, M.D.
Assistant Professor of Pediatrics
Divisions of Hematology-Oncology and Infectious Diseases
Washington University School of Medicine

Peiwen Chen, Ph.D.
Assistant Professor
Department of Neurological Surgery,
Northwestern University

Grant Rowe, M.D., Ph.D.
Assistant Professor of Pediatrics
Harvard Medical School

Min Xue, Ph.D.
Assistant Professor of Chemistry
University of California - Riverside

Hae Lin Jang, Ph.D.
Assistant Professor of Medicine
Brigham and Women's Hospital

Dalnim Cho, Ph.D.
Instructor of Health Disparities Research
The University of Texas MD Anderson Cancer Center

Nilay Sethi, M.D., Ph.D.
Instructor of Medicine
Dana-Farber Cancer Institute

Berkley Gryder, Ph.D.
Assistant Professor
Case Western Reserve University

PEER REVIEWED MEDICAL RESEARCH PROGRAM

Vision: Improve the health, care, and well-being of all military Service Members, Veterans, and beneficiaries

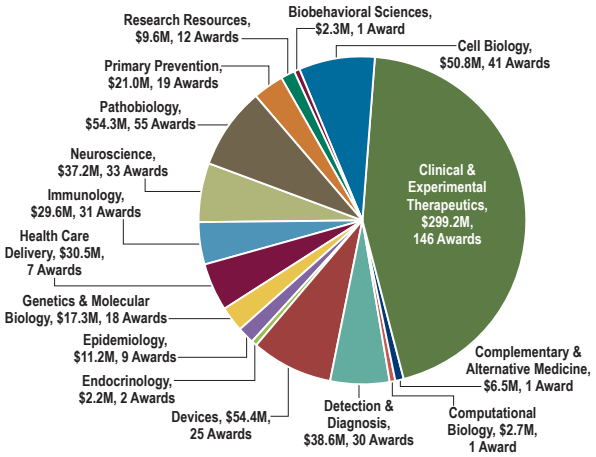
Mission: Encourage, identify, select, and manage medical research projects of clear scientific merit and direct relevance to military health

PROGRAM HISTORY

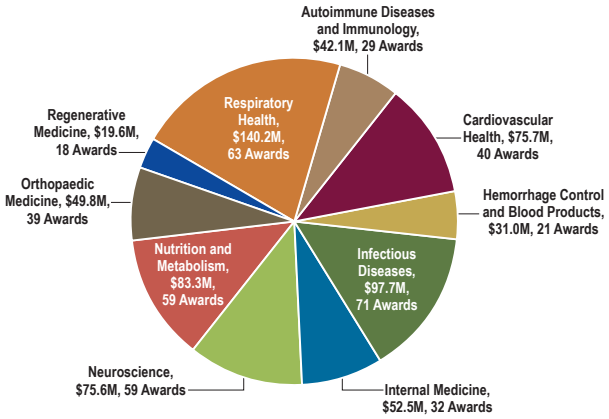
In FY99, Congress established the Peer Reviewed Medical Research Program (PRMRP) to provide support for military health-related research of exceptional scientific merit, toward the goal of improving the health and well-being of military Service Members, Veterans, and their family members. Through its 22-year history, Congress appropriated $3.08B to the program, which supported more than 1,800 research awards in 170 unique Topic Areas representing various diseases and conditions, resulting in over 3,620 peer-reviewed publications and 332 patent applications or patents granted. The FY21 congressional appropriation is $370M to solicit research applications in 42 different Topic Areas.

Research supported by the PRMRP to address near-term needs continues a long tradition of research relevant to military health in response to wartime needs that ultimately benefits Service Members and civilians alike. Service Members, their dependents, and Veterans receive military medical services, creating a critical need to support research on a broad spectrum of medical issues affecting these diverse populations, which include children and the elderly. Supported projects range from exploratory, highly innovative studies to large projects focused on clinical implementation of technologies or interventions.

The PRMRP is committed to funding research that has the potential to profoundly impact the development and implementation of medical devices, drugs, and clinical guidance that will enhance the precision and efficacy of prevention, diagnosis, and treatment across a wide range of disciplines, including autoimmune diseases and immunology, cardiovascular health, hemorrhage control and blood products, infectious disease, internal medicine, neuroscience, nutrition and metabolism, orthopaedic medicine, respiratory health, and regenerative medicine.



FY19-FY20 PRMRP Investment by SCS Code

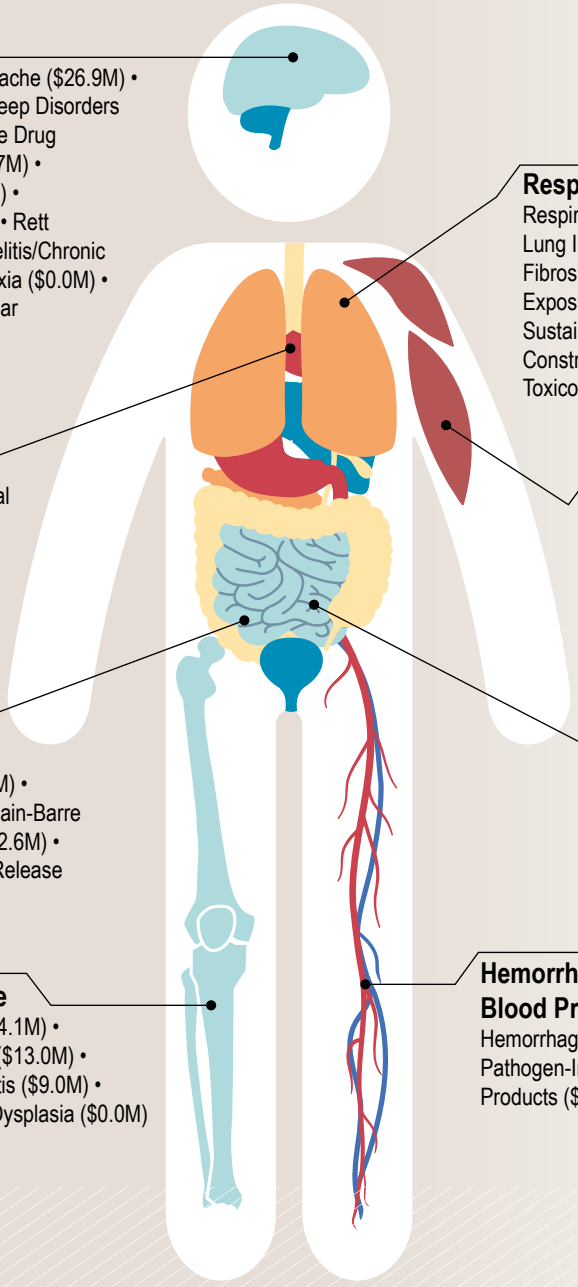


FY19-FY20 PRMRP Investment by Portfolio (431 Awards Totaling $667.4M)

2020 Congressional Appropriations, Research Investment, and Withholds and Management Costs

Congressional Appropriations	Research Investment	Withholds and Management Costs
$360M	Clinical Trial Award ..... $54,774,371 Discovery Award ..... $22,463,536 Expansion Award ..... $31,815,239 Focused Program Award ..... $29,150,975 Investigator-Initiated Research Award ..... $122,288,557 Technology/Therapeutic Development Award ..... $57,756,716 Modifications to ongoing awards..... $12,656,982	USAMRDC ..... $6,768,482 SBIR/STTR ..... $11,695,000 Mgt Costs (3.11%)..... $10,630,142
Total: $360M	**Total:** $330,906,376	**Total:** $29,093,624

FY19 AND FY20 PRMRP TOPIC AREA FUNDING BY PORTFOLIO



Neuroscience
Chronic Migraine and Post-Traumatic Headache ($26.9M) • Frontotemporal Degeneration ($14.5M) • Sleep Disorders and Restriction ($8.0M) • Sustained Release Drug Delivery ($7.8M) • Myotonic Dystrophy ($4.7M) • Dystonia ($3.6M) • Eating Disorders ($2.9M) • Hydrocephalus ($2.6M) • Fragile X ($1.8M) • Rett Syndrome ($1.5M) • Myalgic Encephalomyelitis/Chronic Fatigue Syndrome ($0.5M) • Cerebellar Ataxia ($0.0M) • Resilience Training ($0.0M) • Spinal Muscular Atrophy ($0.0M) • Tinnitus ($0.0M)

Respiratory Health
Respiratory Health ($92.3M) • Acute Lung Injury ($22.1M) • Pulmonary Fibrosis ($21.5M) • Burn Pit Exposure ($3.4M) • Lung Injury ($0.6M) • Sustained Release Drug Delivery ($0.3M) • Constrictive Bronchiolitis ($0.0M) • Metals Toxicology ($0.0M)

Cardiovascular Health
Cardiomyopathy ($29.9M) • Congenital Heart Disease ($25.6M) • Vascular Malformations ($14.2M) • Familial Hypercholesterolemia ($4.8M) • Women's Heart Disease ($1.2M)

Regenerative Medicine
Tissue Regeneration ($10.9M) • Nanomaterials for Bone Regeneration ($6.0M) • Sustained Release Drug Delivery ($2.4M) • Immunomonitoring of Intestinal Transplants ($0.3M)

Autoimmune Diseases and Immunology
Inflammatory Bowel Disease ($20.1M) • Rheumatoid Arthritis ($12.6M) • Guillain-Barre Syndrome ($4.7M) • Scleroderma ($2.6M) • Food Allergies ($2.0M) • Sustained Release Drug Delivery ($0.3M)

Nutrition and Metabolism
Diabetes ($60.5M) • Mitochondrial Disease ($20.8M) • Nutrition Optimization ($2.0M)

Orthopaedic Medicine
Musculoskeletal Health ($24.1M) • Musculoskeletal Disorders ($13.0M) • Post-Traumatic Osteoarthritis ($9.0M) • Arthritis ($3.8M) • Fibrous Dysplasia ($0.0M)

Hemorrhage Control and Blood Products
Hemorrhage Control ($29.6M) • Pathogen-Inactivated Blood Products ($1.3M)

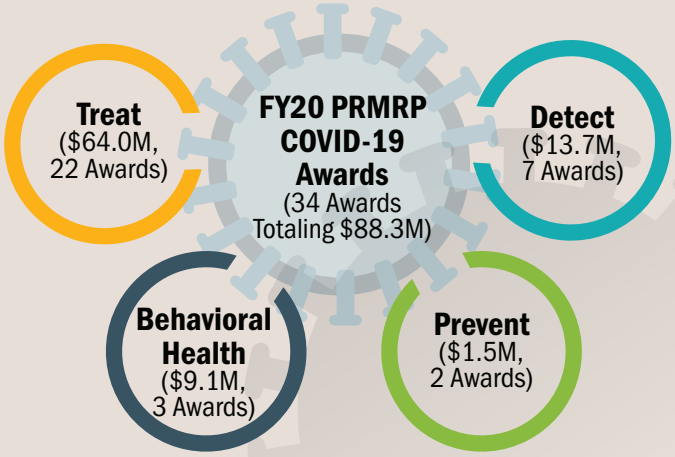
Infectious Diseases
Emerging Viral Diseases ($49.8M) • Antimicrobial Resistance ($16.9M) • Emerging Infectious Diseases ($15.8M) • Hepatitis B ($6.8M) • Tuberculosis ($5.4M) • Sustained Release Drug Delivery ($0.3M) • Plant-Based Vaccines ($0.0M)

Internal Medicine
Polycystic Kidney Disease ($21.2M) • Pancreatitis ($8.7M) • Pressure Ulcers ($8.4M) • Focal Segmental Glomerulosclerosis ($7.6M) • Interstitial Cystitis ($4.4M) • Endometriosis ($2.2M) • Epidermolysis Bullosa ($0.0M) • Hereditary Angioedema ($0.0M)

The PRMRP Augments USAMRDC COVID-19 Research

COVID-19 Response

In response to the Coronavirus Disease 2019 (COVID-19) pandemic, the PRMRP invested $78.3M, using FY20 funding opportunities specifically targeted to support COVID-19 research under the topics of Emerging Viral Diseases and Respiratory Health. These COVID-19-targeted funding opportunities are supporting 24 awards that include clinical trials, advanced development of targeted drugs for potential treatments, and drugs to treat the life-threatening lung injuries associated with COVID-19. The PRMRP also invested $10.0M into 10 COVID-19 research awards that were funded through its traditional FY20 funding opportunities.



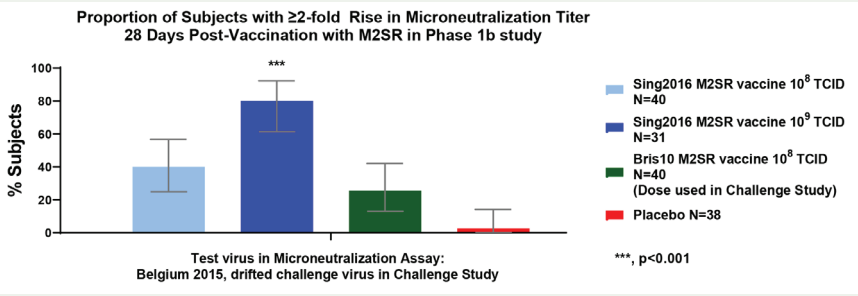
Infectious Diseases

Topic Area: Respiratory Health

With support from an FY19 Focused Program Award to Sanford Burnham Prebys Medical Discovery Institute, Dr. Sumit Chanda is leading an effort to develop broad-spectrum respiratory antivirals that target host cell factors for viral replication or activate components of the innate immune response. The research team is investigating early-stage small molecules with broad-spectrum antiviral activity with the hope of moving several candidates quickly into clinical studies. Upon testing lead compounds for activity against SARS-CoV-2 replication both in vitro and in vivo, Dr. Chanda and his team found that an FDA-approved anti-leprosy drug, clofazimine, had desirable selectivity against SARS-CoV-2 infection and has the potential for treating COVID-19 patients. Based on these initial findings, the group plans to move to phase 2 clinical trials. If successful, these groundbreaking efforts would lead to the development of a new class of antiviral therapeutics for a wide range of infectious diseases, especially those with pandemic potential.

Topic Area: Influenza

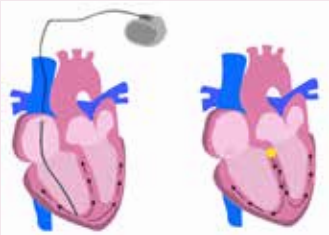
FluGen has developed an alternative live attenuated influenza vaccine to address efficacy issues with current, seasonal influenza vaccines and potentially generate universal protection against the disease. Their M2-deficient single replication (M2SR) vaccine platform initiates infection similar to a wild-type influenza virus, and thus induces a full immune response, without the ability to replicate or spread. In a double-blind, placebo-controlled phase 2 challenge study in healthy adults supported by an FY16 Clinical Trial Award naming Dr. Pamuk Bilsel as the PI, a single intranasal dose of M2SR vaccine produced serum antibody responses in more than half of the treated (i.e., non-placebo) participants. Responders who developed cross-reactive serum microneutralization titers showed reduced viral loads and symptoms after a highly mismatched viral challenge (2007 flu season strain vaccine versus 2014 flu season strain challenge). In a subsequent phase 1b trial, a higher dose level of M2SR induced protective immune responses in a significantly greater proportion of adults, as shown in figure below, indicating the potential for increased protection than that observed in the challenge study. FluGen also received an FY20 Clinical Trial Award to support a randomized double-blind, placebo-controlled phase 1b clinical trial (led by Dr. Bilsel) of H3N2 M2SR in adults over 65 years old to evaluate cross-reactive immune responses in comparison to standard vaccines commonly used in older adults.



Cardiovascular Health

Topic Area: Congenital Heart Disease

With an FY19 Technology/Therapeutic Development Award to Emory University, Dr. Hee Cheol Cho and his team are developing a hardware-free biological pacemaker product to replace the traditional implanted pacemaker. Heart rhythm abnormalities are one of the most common complications for patients with congenital heart disease and often require invasive surgeries to implant cardiac pacing devices. Although these devices can last for up to 10 years in adult patients, pacemakers need to be replaced frequently in pediatric patients due to their faster heart rate and body growth. Dr. Cho's team aims to identify a lead therapeutic product for stable cardiac pacing following a direct comparison of three gene transfer modalities tailored to pediatric and adult congenital heart disease patients. The therapeutic technology, known as BioPace, is a gene therapy designed to provide hardware-free cardiac pacing by converting a tiny region of ordinary heart muscle into natural pacemaker cells. The therapeutic candidates, delivered via a minimally invasive procedure, will undergo a 3-month longitudinal preclinical evaluation to determine safety and efficacy in a large animal model.



Cartoon Representation of BioPace Gene Therapy (Right) Compared to Traditional Cardiac Pacing Device (Left)

Hemorrhage Control and Blood Products

Topic Area: Hemorrhage Control

With support from an FY19 Technology/Therapeutic Development Award to CytoSorbents, Inc., Dr. Maryann Gruda is leading an effort to advance a novel blood group antibody (BGA) adsorption technology, HemoDefend-BGA, to a commercial device for FDA submission. Uncontrolled hemorrhage is a leading cause of trauma-related deaths, especially within the first 24 hours of injury, underscoring the critical need for universal plasma, which is not readily available in all military or civilian emergency settings. The most in-demand, universal plasma products are low titer O whole blood and plasma from individuals with AB blood, because they do not contain anti-A and anti-B antibodies that can bind to the recipient's red blood cells and potentially cause fatal hemolytic reactions. The HemoDefend-BGA adsorber filters and purifies blood by removing anti-A and anti-B antibodies while maintaining essential components like albumin, coagulation factors, red blood cells, and platelets. The commercialization of HemoDefend-BGA will allow for stabilization of and prolonged care for Warfighters with life-threatening hemorrhagic injuries without the need for blood typing.

HemoDefend-BGA Device

Respiratory Health

Topic Area: Acute Lung Injury

Acute respiratory distress syndrome (ARDS) is a life-threatening inflammation of the lungs brought on by factors released after injury or during infection. With support from an FY15 Technology/Therapeutic Development Award to Innovative BioTherapies, Inc., Dr. H. David Humes and his team developed a combat-relevant pig model for acute lung injury (ALI) and assessed the efficacy of selective cytopheretic device therapy (SCDRx) to treat ALI/ARDS. SCDRx involves an immune modulating device shown to be effective in reducing multi-organ dysfunction in critically ill patients by mitigating the inflammatory cascade. The team found that SCDRx demonstrated significant therapeutic benefits in an ALI/ARDS porcine model, which provided evidence to advance this technology into clinical trials. The FDA granted Expanded Access of SCDRx for COVID-19 patients with acute kidney injury and ARDS, and an Investigational Device Exemption multicenter clinical trial is underway. If proven effective, SCDRx could reduce mortality and improve clinical outcomes of critically ill COVID-19 patients and Service Members with deployment-related ALI/ARDS.

PEER REVIEWED ORTHOPAEDIC RESEARCH PROGRAM

Vision: Provide all military Service Members with orthopaedic injuries the opportunity for optimal recovery and restoration of function

Mission: Address the most significant gaps in care for the leading burden of injury and for facilitating return-to-duty by funding innovative, high-impact, clinically relevant research to advance optimal treatment and rehabilitation from musculoskeletal injuries sustained during combat and combat-related activities

PROGRAM HISTORY

Since its inception in 2009, the Peer Reviewed Orthopaedic Research Program (PRORP) has dedicated its congressional appropriations, totaling $458.5M through FY21, to supporting military-relevant orthopaedic research that will also benefit the treatment and care of orthopaedically injured persons in the general population. The PRORP has funded 278 projects (with an additional 20 awards planned by September 30, 2021) that have focused research on orthopaedic topics including treatment, surgical and rehabilitation interventions, prevention of complications, and prosthetics/orthotics.

RELEVANCE TO MILITARY HEALTH

Musculoskeletal conditions affect over 126 million adults in the United States, costing an average of $7,800 per person for treatment.[1] Approximately 1.6 million musculoskeletal injuries occur each year within the DOD, resulting in 2.4 million medical visits and $548M in direct patient-care costs.[2,3] In addition, over half of all combat injuries sustained during OIF and EIF involve extremity injuries and orthopaedic-specific conditions secondary to battle injury, representing the largest source of long-term disability in returning Service Members.[4]

A prospective cohort study of active-duty U.S. Army personnel representing various military units, including Rangers, combat, combat support, and combat Service support found that over half of the participants sustained a musculoskeletal injury during the 12-month study period. Furthermore, over half of all the injuries were located in the lower extremities, and the greatest incidence of injuries and time loss were found in the combat support and combat Service support units.[3] Orthopaedic injuries sustained during combat-related activities tend to be distinct from those seen in the civilian setting and more frequently involve multiple limb trauma, open fractures, major tissue loss, and a high degree of wound contamination. The PRORP is unique in that it supports orthopaedic research for the care of wounded Service Members and Veterans, with projects specific to trauma care. There is a general lack of evidence underlying best practices in trauma care, as these studies are often difficult to conduct and expensive to design and enroll. The PRORP is making a major and meaningful difference in the care of those with extremity injuries by providing funding to support and encourage clinical science for trauma care.

"I believe that input from the consumer advocate plays an invaluable role in the process of researching and developing new treatments and technologies that ultimately benefit us."
Tyler Burdick, Semper Fi Fund, FY18-FY21 Consumer Peer Reviewer

2020 Congressional Appropriations, Research Investment, and Withholds and Management Costs

Congressional Appropriations	Research Investment		Withholds and Management Costs	
$30M	Applied Research Award	$5,796,922	USAMRDC	$579,880
	Clinical Translational Research Award	$12,998,959	SBIR/STTR	$1,006,000
	Clinical Trial Award	$5,518,466	Mgt Costs (4.87%)	$1,698,887
	Modifications to ongoing awards	$2,400,886		
Total: $30M		**Total:** $26,715,233		**Total:** $3,284,767

[1] The Bone and Joint Initiative. "By the Numbers: Musculoskeletal Conditions - Diseases, Disorders, and Injuries Relating to Bones, Joints, and Muscles." https://www.boneandjointburden.org/docs/By%20The%20Numbers%20-%20MSK%20Injuries.pdf

[2] Hauret KG, Jones BH, Bullock SH, et al. 2010. Musculoskeletal injuries: Description of an under-recognized injury problem among military personnel. *American Journal of Preventative Medicine.* 38(1S):S61-S70. https://www.ajpmonline.org/article/S0749-3797(09)00674-6/fulltext

[3] Teyhen DS, Goffar SL, Shaffer SW, et al. 2018. Incidence of musculoskeletal injury in U.S. Army unit types: A prospective cohort study. *Journal of Orthopaedic and Sports Physical Therapy.* 48(10):749-756. https://pubmed.ncbi.nlm.nih.gov/29787695/

[4] Corss JD, Ficke JR, Hsu JR, et al. 2011. Battlefield orthopaedic injuries cause the majority of long-term disabilities. *The Journal of the American Academy of Orthopaedic Surgeons. 19(Suppl. 1):S1-S7.* https://pubmed.ncbi.nlm.nih.gov/21304041/

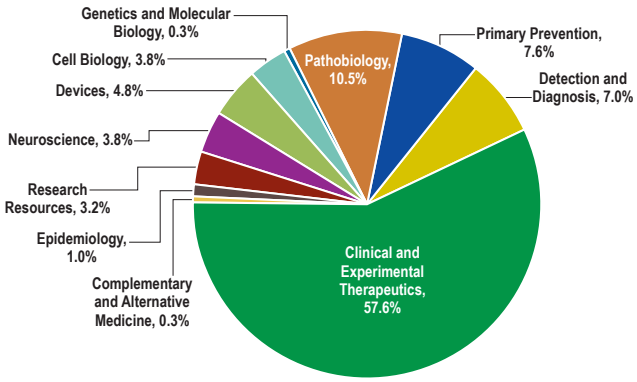
PRORP-FUNDED RESEARCH OUTCOMES (2020-2021)

32 Publications

52 Presentations

2 Patents

PORTFOLIO INVESTMENT



FY09-FY20 PRORP Portfolio Investment

Awards funded by the PRORP between FY09 and FY20 are categorized by scientific area. The largest proportion of the investment is in the Clinical and Experimental Therapeutics area.

FOCUS AREAS

The orthopaedic care field has benefited from many successes; however, many challenges still exist that prevent some injured patients from returning to their pre-injury level of fitness. The research field's ability to address these challenges has a direct impact on the readiness of the U.S. military, the rehabilitation and reintegration of our Veterans, and the clinical care of patients in the general population. To meet this need, the FY21 PRORP requires all applications to address at least one of the following PRORP Focus Areas:

- Compartment Syndrome
- Limb Stabilization and Protection
- Osseointegration
- Prosthetic and Orthotic Devices
- Retention Strategies for Battlefield Care or to Facilitate Return to Duty
- Tissue Regeneration Therapeutics
- Translation of Early Findings in Soft Tissue Trauma or Fracture-Related Infection

NEW CLINICAL TRIALS IN 2020

Accelerating Recovery Following a Lower Extremity Fracture Through Speed High Intensity Interval Training (HIIT)
Principal Investigator: Brian Noehren, P.T., Ph.D., University of Kentucky

Blood Flow Restriction Therapy for the Postoperative Rehabilitation of Anterior Cruciate Ligament Reconstruction with Quadriceps Tendon Autograft
Principal Investigator: Andrew Sheean, M.D., U.S. Brooke Army Medical Center

Does Prophylactic Local Tobramycin Injection Lower Open Fracture Infection Rates?
Principal Investigator: Arun Aneja, M.D., Ph.D., University of Kentucky

Nerve Repair with Polyethylene Glycol to Promote Rapid Return of Nerve Function
Principal Investigator: Wesley Thayer, M.D., Ph.D., Vanderbilt University Medical Center

Oxandrolone Supplementation in Trauma: The Post-Injury Trial
Principal Investigator: Scott Tintle, M.D, Walter Reed National Military Medical Center (WRNMMC)

Prophylactic Antibiotic-Coated Nail to Prevent Infection: A Clinical Trial
Principal Investigator: Joseph Hsu, M.D., Atrium Health

Regenerative Peripheral Nerve Interfaces to Treat Painful Digit and Hand Neuromas After Amputation: A Randomized, Prospective Study
Principal Investigator: Aviram Giladi, M.D., MedStar Health Research Institute

PROSTATE CANCER RESEARCH PROGRAM

Vision: Conquer prostate cancer

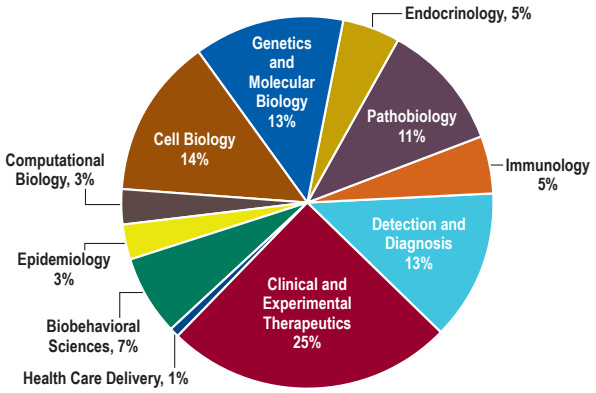
Mission: Fund research that will lead to the elimination of death from prostate cancer and enhance the well-being of Service Members, Veterans, and all men experiencing the impact of the disease

PROGRAM HISTORY

Since its inception in 1997 and over its 24-year history of congressional support totaling nearly $2.04B, the Peer Reviewed Prostate Cancer Research Program (PCRP) has changed the landscape of biomedical research and energized the prostate cancer (PCa) research community to conduct high-risk research that is decidedly collaborative, innovative, and impactful, ultimately aiming to conquer the disease. The PCRP made unprecedented inroads in supporting the development of new treatments for advanced PCa. It is the leading supporter of research aimed at understanding and resolving health disparities in PCa incidence and mortality and has fostered the development of over a thousand young investigators, many of whom have become leaders in cutting-edge research that is making a significant difference for millions of patients with PCa.

INVESTMENT STRATEGY

The PCRP strategically targets underfunded areas critical to conquering prostate cancer by identifying gaps in the prostate cancer research funding landscape. Investing in a wide range of funding mechanisms (Research Investment table) and research disciplines (Portfolio pie chart) enables the program to address the PCRP Overarching Challenges with a variety of research approaches. The program continuously analyzes the outcomes of PCRP-funded projects to assess progress in addressing the overarching challenges, mission, and vision, and revises the investment strategy as needed.



FY18-FY20 PCRP Portfolio Investment by SCS Code

"Four and a half years ago my prostate-specific antigen (PSA) was doubling. every appointment. With newer hormone therapies available, we decided to try XTANDI (enzalutamide). For the next 4 years my cancer was almost undetectable, which was a godsend for my wife and myself. It was easy to take four pills a day and I had no side effects. Even though my cancer recently stopped responding to the treatment, I would not still be here today if it weren't for this therapy that was developed with PCRP funding."

Peter Roberts, Save Your Males, FY17-FY20 Consumer Peer Reviewer

2020 Congressional Appropriations, Research Investment, and Withholds and Management Costs

Congressional Appropriations	Research Investment	Withholds and Management Costs
$110M	Clinical Trial Award ..... $3,082,636 Early Investigator Research Award ..... $8,885,724 Health Disparity Research Award ..... $13,134,572 Idea Development Award ..... $40,945,077 Idea Expansion Award ..... $4,486,183 Modifications to ongoing awards ..... $3,686,458 Physicians Research Award ..... $6,812,485 Population Science and Outcomes Research Award ..... $3,784,721 Translational Science Award $13,116,770	USAMRDC ..... $2,100,885 SBIR/STTR ..... $3,690,000 Mgt Costs (6.02%) . $6,274,488
Total: $110M	**Total:** $97,934,626	**Total:** $12,065,373

IMPACTING PATIENTS IN THE MILITARY HEALTH SYSTEM

PCRP investments in new therapies have led to FDA-approval of treatments that are now standard of care and are broadly impacting PCa patients, including those treated in the MHS. Over 9,000 patients in the MHS, including active-duty Service Members and Veteran retirees, have benefited from treatment with these drugs, with a total number of 103,224 prescriptions written since these agents were FDA-approved.

OVERARCHING CHALLENGES

In 2018, the PCRP developed a strategic plan that outlines the program's 5-year strategy for funding innovative and impactful ideas that will ultimately lead to the elimination of death from prostate cancer. At the heart of the PCRP Strategic Plan are four overarching challenges that the PCRP is working to address with the available appropriations. Recent advancements addressing each of the PCRP Overarching Challenges are:

Improve quality of life to enhance outcomes and overall health and wellness for those impacted by prostate cancer

Drs. Tien Liu and Ashesh Jani collaborated to preserve sexual function in men undergoing radiation treatment for prostate cancer by combining magnetic resonance imaging (MRI) and ultrasound in order to better visualize neurovascular bundles surrounding the prostate to spare nerve damage, preserve sexual function, and improve quality of life.

Define the biology of lethal prostate cancer to reduce death

Dr. Wassim Abida and his research on identifying genomic drivers of prostate cancer progression, specifically his work on understanding and targeting mutations in the DNA repair genes BRCA1 and BRCA2, contributed to the clinical trial leading to the 2020 FDA approval of the poly (ADP-ribose) polymerase (PARP) inhibitor rucaparib for metastatic prostate cancer.

Develop treatments that improve outcomes for men with lethal prostate cancer

Research by Drs. Paul Fischer and Xian-Yang (Shawn) Wang revealed a new approach to immunotherapy by engineering T cells to deliver MDA-7, the gene coding for IL-24, to both primary tumor cells and its deadly metastases. After securing additional outside funding, Drs. Fischer and Wang are now optimizing their technology in anticipation of future human trials.

Advance health equity and reduce disparities in prostate cancer

Drs. Peter Gann and Adam Murphy have recently shown that in an urban patient population of predominantly black men with substantial social disadvantage, men with low health literacy were less likely to choose active surveillance following tumor profiling. Active surveillance is a preferable approach to monitor low-risk tumors before more aggressive treatments, highlighting the need for health education efforts in disparate communities so low-risk patients can make informed treatment decisions.

"The PCRP has transformed the research portfolio of the prostate cancer community over the last decade. Specifically, it has championed the funding of cutting-edge, out-of-the-box ideas and projects without requiring large amounts of preliminary data. These Idea Awards, coupled with the funding of new investigators and trainees, has ensured a robust pipeline of new investigators to the prostate cancer battle."

Ken Pienta, M.D., Johns Hopkins University School of Medicine, FY21 Programmatic Panel Chair

RARE CANCERS RESEARCH PROGRAM

Vision: To greatly improve outcomes for people with rare cancers through discovery and community building, and expansion of knowledge across the cancer landscape

Mission: Elevate rare cancers research to enable clinically impactful discoveries for the benefit of Service Members, their families, Veterans, and the American public

PROGRAM HISTORY

Rare cancers pose unique challenges to patients, clinicians, and researchers because of limited resources, information, therapeutics, and in-depth knowlege – specifically, lack of available patient tissues, cell and tumor models for research; lack of understanding of the tumor biology and cell of origin of rare cancers; lack of infrastructure for sharing data and other resources; and lack of collaboration among the stakeholders to advance rare cancers research needs. Rare cancer patients are almost seven times less likely to have an approved targeted therapy compared to patients with other cancers. As of November 2018, over 100 rare cancers had no publicly available datasets on the Gene Expression Omnibus repository, a major source of publicly available data.[1] Congress directed $7.5M specifically to rare cancers research in the FY20 DOD appropriation and established the Peer Reviewed Rare Cancers Research Program (RCRP). The RCRP defines rare cancer as cancers affecting less than 6 persons per 100,000 per year in the U.S.[2] In FY21, the congressional appropriation for the RCRP was increased to $17.5M.

Prior to the initiation of the RCRP in FY20, rare cancers research was first introduced as a Topic Area under the Peer Reviewed Cancer Research Program (PRCRP) in FY19. To date, the PRCRP has funded several rare cancer types/subtypes,[3] totaling over $90M. Various rare cancers Topic/Sub-Topic Areas have been awarded by the Breast Cancer Research Program (FY92-FY19), Melanoma Research Program (FY19), and the Ovarian Cancer Program (FY99-FY19), totaling over $20.47M.

"As the Chair of the Department of Neurology at the Uniformed Services University of the Health Sciences and as a Neuro-Oncologist at the Murtha Cancer Center at WRNMMC and NIH/NCI Neuro-Oncology Branch, I am honored to be a member of the inaugural Programmatic Panel for the RCRP. Even the most common brain cancers, for example glioblastoma, meet current definitions for rare and orphan diseases. The active-duty military population has a large population aged between 18 and 40 years. The active-duty population group encompasses the Adolescent and Young Adult (AYA) population, which is understudied as a whole and in which rare cancers are among the most common causes of cancer-related morbidity and mortality. The RCRP is yet another example of the dedicated mission of the CDMRP, with support from the DOD, to fund basic, translational, and clinical research in cancers that impact both the active-duty and civilian populations."

LTC Brett J. Theeler (U.S. Army), M.D., WRNMMC, FY20-FY21 Programmatic Panel Member

2020 Congressional Appropriations, Research Investment, and Withholds and Management Costs

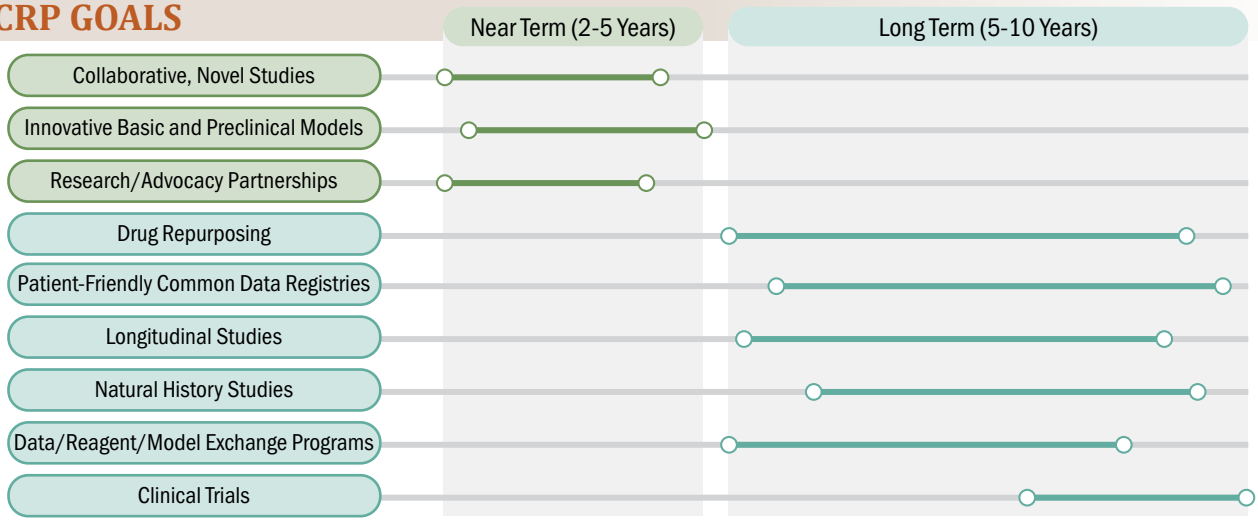
Congressional Appropriations	Research Investment		Withholds and Management Costs	
$7.5M	Concept Award	$1,319,903	USAMRDC	$144,960
	Idea Development Award	$3,731,914	SBIR/STTR	$252,000
	Resource Community Development Award	$1,568,094	Mgt Costs (6.8%)	$483,130
Total: $7.5M		**Total:** $6,619,910		**Total:** $880,090

[1] Rare Cancer's "Valley of Death," American Association of Cancer Researchers, Abstract 2505, Atlanta, 2019.
[2] DeSantis CE. 2017. The burden of rare cancers in the United States. *CA Cancer J Clin*, 67:261-272. https://acsjournals.onlinelibrary.wiley.com/doi/pdf/10.3322/caac.21400
[3] Rare cancer types/subtypes with less than 6 incidence rate per 100K, and are representative of FY20 Peer Reviewed Cancer Research Program topics.

"As the parent of a pediatric brain tumor survivor, I feel incredibly honored to be a member of the RCRP panel. The RCRP's inclusion of individuals who are impacted by a rare cancer disease on a deeply personal level is evidence of their commitment to fully understand the effect of rare cancers on patients and their families. The mission and vision of the RCRP gives me hope for a better future for patients like my son and the families who love and care for them."

Lori Stephen, LCSW-C, National Brain Tumor Society, FY20-FY21 Programmatic Panel Member

RCRP GOALS



RCRP AWARD MECHANISMS

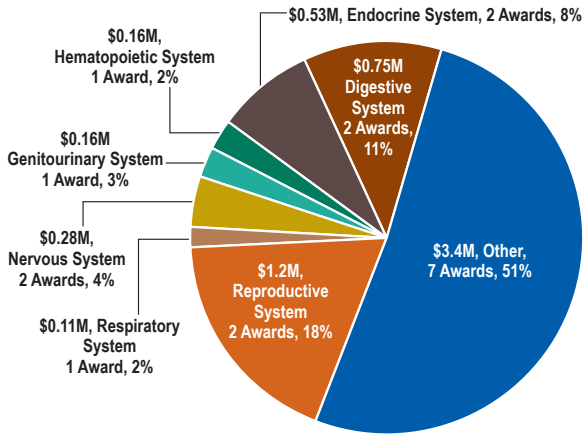
Award Mechanism	Key Elements	Direct Costs	Period of Performance
Concept Award	Supports development of highly innovative, untested, and potentially groundbreaking concepts in a rare cancer field.	$100,000	1 year
Idea Development Award	Supports innovative and high-risk/high-reward research with the potential to yield impactful data in the rare cancer field.	$350,000	3 years
Resource and Community Development Award	Supports research resources development to facilitate collaboration and information sharing among stakeholders such as researchers, patients, caregivers, clinicians, and other members of the rare cancers community.	$600,000	3 years

RESEARCH HIGHLIGHT

Dr. Jesse Boehm at the Massachusetts Institute of Technology received an FY20 Resource Community Development Award to develop a broadly available resource of genomically characterized rare soft tissue sarcomas. Using a direct-to-patient platform for living tissue donation, the team will collect tissue samples from patients with desmoid tumors, clear cell sarcomas, and leiomyosarcoma. Cell line models will be created for these rare soft tissue sarcomas and characterized via whole-exome sequencing, RNA-sequencing, and in some instances, single-cell RNA-sequencing. The final goal of the project is to demonstrate proof-of-concept for the discovery of therapeutic targets via genome-wide Cas12a dependency screens. Successful completion of this project will create new resources for the sarcoma community to leverage new models and data to improve understanding of the rare sarcomas and facilitate drug discovery.

RCRP INVESTMENTS

In FY20, the RCRP funded 18 awards, totaling $6.61M. Below is the breakdown by ACS (American Cancer Society) system classification.



FY20 RCRP Portfolio Investment by ACS System Classification

RECONSTRUCTIVE TRANSPLANT RESEARCH PROGRAM

Vision: Reconstructive transplant: An accessible reality and viable choice

Mission: Advance science, education, and clinical practice of vascularized composite allotransplantation to improve access and safety; implement a standardized and comprehensive approach for consideration of all variables influencing outcomes of VCA for catastrophically injured Service Members, Veterans, and American civilians

PROGRAM HISTORY

In 2012, Congress initiated the The Peer Reviewed Reconstructive Transplant Research Program (RTRP) to provide support for research of exceptional scientific merit that has the potential to make a significant impact on improving the function, wellness, and overall quality of life for injured military Service Members and Veterans, their caregivers and family members, and the American public. Appropriations for the RTRP from FY12 through FY20 totaled $105M. The FY21 appropriation is $12M.

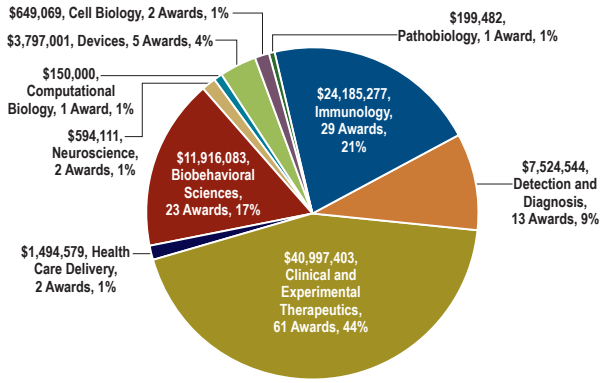
The RTRP challenges the scientific community to design innovative research that will expand reconstructive options for catastrophically injured Service Members, Veterans, and American civilians by developing a standardized conduct of vascularized composite allotransplantation (VCA) procedures. VCA refers to the transplantation of multiple tissues such as muscle, bone, nerve, and skin, as a functional unit (e.g., a hand or face) from a deceased donor to a recipient with a severe injury. The ultimate goal is to return injured Service Members to duty and restore their quality of life.

RTRP FY21 Investigator-Initiated Research Award Focus Areas

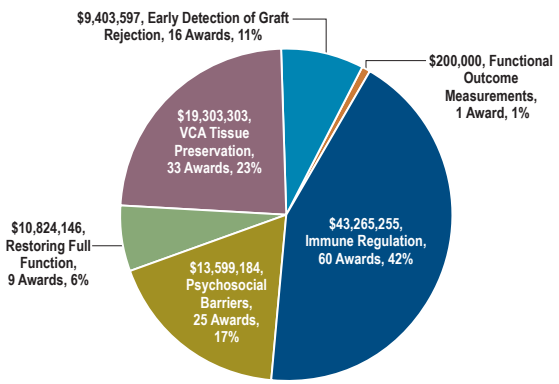
- Reduce the risks of VCA-associated immunosuppression.
- Develop reliable non-invasive prognostic/diagnostic biomarkers, or methods or tools, for monitoring VCA graft rejection, including applications that would be suitable for point-of-care testing or home monitoring.
- Retrospective studies for VCA.

RTRP FY21 Advanced Technology Development Award Focus Areas

- Advance existing ex vivo tissue preservation strategies to extend the timeline between procurement and transplantation.
- Advance reliable non-invasive prognostic/diagnostic biomarkers, or methods or tools, for monitoring VCA graft rejection, including applications that would be suitable for point-of-care testing or home monitoring.



FY12-FY20 RTRP Portfolio Investments by SCS Code



FY12-FY20 RTRP Portfolio Investments by Barrier

2020 Congressional Appropriations, Research Investment, and Withholds and Management Costs

Congressional Appropriations	Research Investment	Withholds and Management Costs
$12M	Investigator-Initiated Research Award .....$9,496,106 Modifications to ongoing awards.....$857,361	USAMRDC ..... $231,940 SBIR/STTR .....$403,000 Mgt Costs (8.9%) ... $1,011,593
Total: $12M	**Total:** $10,353,467	**Total:** $1,646,533

https://cdmrp.army.mil/cwg/stories/2021/joe_kinan_profile

JOE KINAN: A STORY OF A DEVASTATING FIRE AND A REMARKABLE TRANSPLANTATION

Joe Kinan rearranged his work schedule to attend a local concert at The Station nightclub in Warwick, RI, on the night of February 20, 2003. Within seconds the band's pyrotechnics display caught fire to the building, and over 400 attendees rushed to escape. Joe's friend was one of 100 people who lost their lives that night, and Joe was one of 230 who were injured. He sustained third and fourth degree burns over 40% of his body, on his head, face, and arms, losing all of his fingers, both ears, and sight in one eye. Over the next year, he endured over 150 surgeries and procedures.

Joe was referred to Dr. Curtis Cetrulo at Massachusetts General Hospital, where he learned of the possibility of hand transplantation and underwent evaluation to become listed for a hand transplant. A team of 20 surgeons led by Dr. Cetrulo transplanted a donor hand onto Joe's left arm in a 17-hour procedure. This was followed by immunosuppression to protect against graft rejection, and intensive rehabilitation. Despite several rejection episodes, Joe recovered well. Joe fondly recalls the exciting moment when he was able to pour his own cup of coffee independently. He also enjoys holding hands with his wife, playing with his daughter, and cooking. Joe's firsthand experience serves him well in his role as a consumer reviewer for the RTRP program.

RESEARCH HIGHLIGHTS

Predicting Post-Transplant Function and Outcomes for Upper Extremity Transplantation

Simon Talbot, M.D., Brigham and Women's Hospital

As upper extremity VCA (UE-VCA) moves from an experimental option to more routine, it becomes important to identify psychosocial factors that impact transplant success and failure. Dr. Talbot and his team at Brigham and Women's Hospital received an FY16 Qualitative Research Award to determine the psychosocial variables associated with hand transplant outcomes.

The team studied data available from the International Registry on Hand and Composite Tissue Transplantation and psychosocial surveys retrospectively completed by the transplant centers on 43 UE-VCA recipients. Surveys focused on recipient's psychosocial health, including depression, anxiety, medication compliance, social support, and post-transplant expectations. Statistical analysis identified transplant recipients with anxiety, depression, and symptoms of PTSD as more likely to have undergone transplant removal. They also found that UE-VCA recipients who did not actively participate in their rehabilitation had a nearly threefold increased risk of transplant removal. In contrast, recipients with realistic expectations regarding post-transplant function and those with a strong social support network of friends/family had a lower chance of transplant removal. In the second phase of their study, the team is currently working directly with upper extremity transplantation recipients and expert clinicians to identify the key variables affecting transplant outcomes.

First Successful Face and Double Hand Transplant Using 3D-Modeling-Based Surgical Approach

Daniel Ceradini, M.D., New York University Langone Medical Center

Dr. Daniel Ceradini of New York University Langone Medical Center received an FY15 RTRP award to conduct a clinical trial investigating the utility of 3D modeling for surgical planning of facial transplantation and 3D-printed patient-specific cut guides for optimizing functional and aesthetic outcomes in face transplantation. Surgical time was reduced by up to 60% as a result of these cutting-edge procedures for the three patients enrolled in this clinical trial.

The most recent patient received not only a face transplant, but also a double hand transplant. Twenty-two-year old Joe DiMeo is the first successful face and double hand transplant recipient in the world. A team of 140 medical professionals completed these procedures in 23 hours. Joe is very determined to recover and has participated in as much as 5 hours of rehabilitation per day. Nearly 1 year after receiving his transplants, Joe continues to do very well. Although now closed to enrollment, the clinical trial will continue for another year to monitor the patients. Another goal of the study is to identify predictive markers for acute graft rejection, which is being examined by collecting samples during periods of rejection and non-rejection.

SCLERODERMA RESEARCH PROGRAM

Vision: To combat scleroderma through a partnership of scientists, clinicians, and consumers

Mission: To fund and facilitate the most promising, highest quality research aimed at understanding mechanisms, improving therapies, and ultimately curing scleroderma for Service Members, Veterans, and the American public

PROGRAM HISTORY

Scleroderma, or systemic sclerosis (SSc), is a poorly understood heterogeneous rare autoimmune disease. Scleroderma presents as a chronic connective tissue multisystem disorder characterized by vasculopathy, autoimmunity, inflammation, and fibrosis. Currently there are no validated biomarkers or effective disease-modifying treatments for scleroderma. As a result, patient survival is poor, leading to scleroderma having the highest mortality rate of any systemic autoimmune disease.

To address the significant research gaps in scleroderma, Congress directed $5M to establish the Peer Reviewed Scleroderm Research Program (SRP) in FY20. The SRP has received $10.0M in congressional appropriations through FY21. In its inaugural year, the FY20 SRP funded 10 awards representing 5 unique projects addressing a subset of Overarching Challenges facing the scleroderma community (Table 1). Table 2 describes the research Areas of Emphasis used by the SRP to address the Overarching Challenges.

Table 1: SRP Overarching Challenges

Understanding Cell Biology
Understanding Disease Heterogeneity
Identifying Therapeutic Targets
Conducting Clinical Trials
Addressing Quality of Life and Survivorship

Table 2: SRP FY20 Research Areas of Emphasis

Development of clinical trial platforms that enable the rapid comparison of different therapeutic approaches on a pilot basis.
Define biomarkers (e.g., -omics and/or molecular markers, cell subsets, imaging, patient-reported outcomes) that help inform therapeutic choices (immunosuppressive/anti-fibrotic) or predict disease course (morbidity) and quality of life.
Secondary analysis of scleroderma and other similar disease datasets to identify novel targets and biomarkers that can be validated in existing or new models.
Understanding the different biological/metabolic pathways that differentiate subsets of patients (e.g., gender, age, genetic, clinical phenotype, race/ethnicity).
Utilizing systems biology and multi-omics approaches to understand the heterogeneity of disease, prevention, therapeutics inventions, and screening.
Development of cohorts from diverse populations (longitudinal) to validate potential biomarkers (i.e., replication studies).
Defining epigenetic changes, multiple cell types, and molecules that mediate pathogenesis.

"I have been so impressed by my experience with CDMRP and the genuine respect and support they give the consumer reviewers. I have met many of the consumer reviewers over the past few years and we come from an array of backgrounds. The team leading the CDMRP review program has thoroughly prepared us for our roles and instilled confidence that our voice matters and that our input is as valuable as the scientific reviewers' input."

Karen Kemper, Ph.D., Scleroderma Foundation, FY20-FY21 Consumer Peer Reviewer

2020 Congressional Appropriations, Research Investment, and Withholds and Management Costs

Congressional Appropriations	Research Investment	Withholds and Management Costs
$5M	Idea Development Award ..... $465,504 Idea Development Award – New Investigator Collaboration Option..... $1,459,112 Translational Research Partnership Award $2,504,649	USAMRDC ..... $46,176 SBIR/STTR ..... $168,000 Mgt Costs (7.45%) $356,559
Total: $5M	**Total:** $4,429,265	**Total:** $570,735

In its inaugural year, the FY20 SRP funded 10 awards representing 5 unique projects through 2 award mechanisms: Idea Development Award and Translational Research Partnership Award.

The research projects below represent the promising research supported by the SRP.

IDEA DEVELOPMENT AWARD

microRNA of Circulating Exosomes for Systemic Sclerosis
Sergio Jimenez, M.D., Thomas Jefferson University
A major unmet need for SSc clinical management is the absence of well-validated biomarkers that allow for early diagnosis and accurate assessment of SSc-associated pulmonary fibrosis. Dr. Jimenez will analyze differentially expressed biomarkers isolated from SSc patient blood to accurately differentiate patients with SSc from non-SSc patients, and patients with SSc-associated interstitial lung disease (ILD) from patients without SSc-associated ILD.

IDEA DEVELOPMENT AWARD – NEW INVESTIGATOR COLLABORATION OPTION

Defining the Effects of Autologous Stem Cell Transplant on the Cellular and Transcriptomic Landscape of Juvenile Systemic Sclerosis
Kathryn Torok, M.D., University of Pittsburgh
Jessie Barnum, M.D., University of Pittsburgh
Juvenile-onset systemic sclerosis (jSSc) is a rare, life-threatening autoimmune disease. While jSSc resembles adult-onset SSc, much remains unknown. Drs. Torok and Barnum will analyze cellular and transcriptomic differences in the expression profile of jSSc peripheral blood cells and skin before and after autologous stem cell transplant in an effort to identify key molecular changes involved in jSSc disease.

Biomarkers and Pathogenesis of Cutaneous Fibrosis
Robert Lafyatis, M.D., University of Pittsburgh
Rachel Rosenstein, M.D., Ph.D., Hackensack University Medical Center
Drs. Lafyatis and Rosenstein aim to identify blood biomarkers of cutaneous fibrosis and new drug targets. By investigating the early steps in the pathogenesis of sclerotic chronic graft-versus-host disease, they hope to shed light on the roles of T cells in the development of skin fibrosis.

TRANSLATIONAL RESEARCH PARTNERSHIP AWARD

Cytotoxic CD8 T-Cell Subsets in Scleroderma Lung Disease
Francesco Boin, M.D., Cedars-Sinai Medical Center
Deepak Rao, M.D., Ph.D., Brigham and Women's Hospital
Pulmonary disease is a major cause of morbidity and mortality in SSc, yet the key immune mechanisms driving lung damage in SSc remain unclear. Drs. Boin and Rao's project aims to define the function, development, and gene expression patterns of a unique cluster of CD8 T cells thought to contribute to lung injury in SSc.

A Molecular Classification Paradigm to Predict Therapeutic Response in Systemic Sclerosis
Michael Whitfield, Ph.D., Dartmouth College
Dinesh Khanna, M.B.B.S., University of Michigan
Fred Kolling IV, Ph.D., Dartmouth College
Dr. Whitfield and his collaborators aim to develop a precision-medicine stratification tool that can be used to analyze peripheral blood cell samples from SSc patients. RNA profiling of PBCs from SSc patients involved in the phase 2 trial of abatacept (ASSET trial) will identify histological features that differentiate patient subgroups and lead to predicted therapeutic response.

SPINAL CORD INJURY RESEARCH PROGRAM

Vision: Advance the treatment and management of spinal cord injury and ameliorate its consequences relevant to injured Service Members

Mission: To fund research and encourage multidisciplinary collaborations for the development and translation of more effective strategies to improve the health and well-being of Service Members, Veterans, and other individuals with spinal cord injury

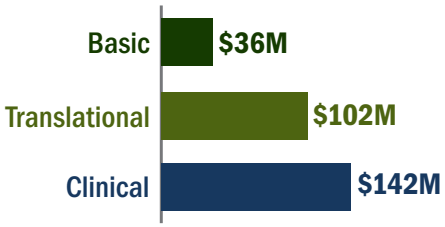
PROGRAM HISTORY

Spinal cord injuries (SCIs) are complex neurotraumatic wounds with long-term consequences requiring lifelong care. It is estimated that about 300,000 individuals are living with an SCI,[1] and this number continues to grow, as over 17,000 new cases occur in the U.S. each year. ***This means on average, someone in the U.S. suffers an SCI every 30 minutes.***

Congress established the Peer Reviewed Spinal Cord Injury Research Program (SCIRP) in FY09 to support research and treatments into repairing/regenerating damaged spinal cords and improving rehabilitation therapies. With $357.85M in congressional appropriations between FY09 and FY21 for peer-reviewed spinal cord research, the SCIRP supports the translation of therapeutic strategies across the continuum of care from management of the acute injury through functional and psychological rehabilitation for chronically injured individuals.

PROGRAM PORTFOLIO

The SCIRP funded 278 awards through FY20 across the research and development continuum but favors projects in a more advanced stage of development, with over $140M invested into projects that are touching patients now.



CURRENT PROGRAM PRIORITIES

The program evaluates its priorities annually, in partnership with members of the SCI community, researchers, clinicians, and other funders. The FY21 program priorities are listed below:

- Preserving and protecting spinal cord tissue at time of injury for improved neurologic outcomes
- Identifying and validating biomarkers for diagnosis, prognosis, and for evaluation of treatment efficacies
- Bowel, genitourinary, cardiopulmonary dysfunction, and neuropathic pain
- Psychosocial issues relevant to people with SCI, their families, and/or their care partners
- Rehabilitation and regeneration – maximizing the function of the residual neural circuitry, including harnessing neuroplasticity and recovery to improve function after SCI

EXCITING NEW RESEARCH

- Dr. Laura Carbone - Augusta University Research Institute - Clinical testing of a novel non-opioid strategy for treating neuropathic pain
- Dr. Jae Lee - University of Miami - Discovering novel anti-inflammatory drugs for neuroprotection post-SCI
- Dr. Rachel Cowan - University of Alabama - Determining meaningful changes in fitness and their relation to changes in self-care, mobility, and independence for individuals with SCI
- Dr. Chad Swank - Baylor Scott & White Research Institute - Investigating the benefits of exoskeleton assisted walking in the first months of recovery

2020 Congressional Appropriations, Research Investment, and Withholds and Management Costs

Congressional Appropriations	Research Investment	Withholds and Management Costs
$40M	Clinical Trial Award ..... $11,601,777 Expansion Award ..... $8,419,407 Investigator-Initiated Research Award ..... $9,267,980 Translational Research Award ..... $5,375,663 Modifications to ongoing awards..... $1,041,405	USAMRDC ..... $763,656 SBIR/STTR ..... $1,341,000 Mgt Costs (5.78%) . $2,189,112
Total: $40M	**Total:** $35,706,232	**Total:** $4,293,768

[1] https://www.nscisc.uab.edu/

FY21 RESEARCH OUTCOMES

SCIRP is a program addressing congressional intent for an SCI research and treatment program looking to develop healthcare solutions for and in partnership with the SCI community. Below are examples of some of the amazing research accomplishments from 2021.

PSYCHOSOCIAL ISSUES

Dr. Allen Heinemann at the Shirley Ryan Ability Lab leads an FY16 SCIRP Qualitative Research Award utilizing patient focus groups to examine how robotic exoskeleton technology is received in the SCI community, with the ultimate goal of leveraging consumer experiences to establish recommendations and regulations for exoskeleton use. Exoskeleton users emphasized the psychological benefits of being eye-level with their non-disabled friends and family, and some reported physiologic improvements in areas such as bowel/bladder function and pain management. Despite these benefits, participants reported several drawbacks such as safety concerns, fatigue, muscle spasms, device size, and inaccessibility for the average user. Dr. Heinemann's research highlights that exoskeletons are promising mobility aids but have a long way to go before widespread adoption by the SCI community. Most importantly, this user-focused research demonstrates the critical need to center the lived experiences of those with SCI for the successful adoption of rehabilitative technologies.

REHABILITATION AND REGENERATION

Stentrode™ was selected as one of the 100 Best Inventions of 2021 by Time Magazine

Brain-computer interfaces (BCI) aim at establishing a direct link to the brain and may provide a bridge to restoring independent function and limb control. Dr. Nicholas Opie of the University of Melbourne leveraged an FY16 SCIRP Translational Research Award to provide crucial development, optimization, and biosafety testing of the Stentrode™. This novel BCI technology is unique in that it uses a minimally invasive endovascular (in vein) delivery method, thereby overcoming many of the limitations of traditional approaches. The SCIRP-funded project was integral for an industry-funded first-in-human clinical trial in individuals with motor deficits and severe paralysis. In this clinical trial, after an initial training period with the technology, participants regained their ability to perform independent activities of daily living, such as communication, using a computer and smart phone to text, send emails, shop online, and for banking. This provides not just proof of concept for the endovascular BCI, but real hope for individuals living with neurological disorders or injuries to regain meaningful independence and autonomy. The company developing the Stentrode, Synchron, recently received FDA approval to commence human trials in the United States.

BIOMARKERS

Imaging is a critical diagnostic and prognostic tool for clinicians, particularly for CNS injuries. After a traumatic SCI, metal hardware is often implanted to stabilize the injury. However, this limits the ability to perform MRI near the implanted hardware. With an FY18 SCIRP Investigator-Initiated Research Award to the Medical College of Wisconsin, Dr. Kevin Koch is focusing on using multispectral imaging to reduce the signal disruption around metal hardware in SCI patients to allow for more accurate imaging of the spinal cord. Importantly, metal hardware implantation is not restricted to SCIs, and optimized imaging techniques around metal fixators would have widespread benefit for Service Members and civilians recovering from orthopaedic injuries as well.

TICK-BORNE DISEASE RESEARCH PROGRAM

Vision: To prevent the occurrence, better diagnose, and resolve or minimize the impact of Lyme disease and other tick-borne illnesses, with emphasis on burden of disease

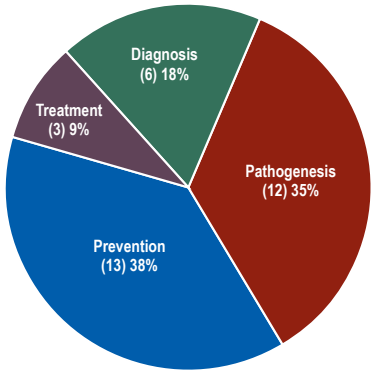
Mission: To understand the pathogenesis of Lyme disease and other tick-borne illnesses, to deliver innovative solutions to prevent, diagnose, and treat their manifestations for the benefit of U.S. Service Members and the American public, and to disseminate this knowledge

PROGRAM HISTORY

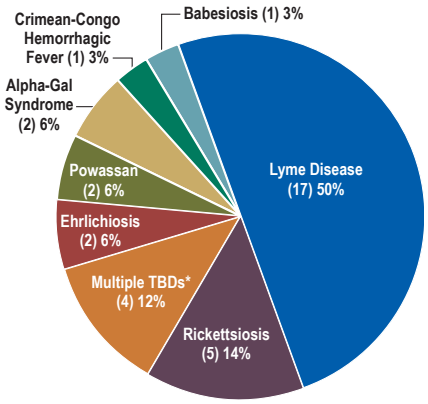
The efforts of Lyme disease advocates led to a congressional appropriation of $5M in FY16, establishing the Peer Reviewed Tick-Borne Disease Research Program (TBDRP). The TBDRP has received funding totaling $27M for the period FY16-FY20. In FY21, the TBDRP appropriation is $7M. Each year, with input from the peer and programmatic review panels, the TBDRP strives to maximize its investment by supporting research that is innovative and impactful and aims to address fundamental knowledge gaps in the field of tick-borne diseases (TBDs).

Currently, there are at least 18 known infectious tick-borne pathogens, resulting in 20 conditions and 13 illnesses.[1] Diagnosis and treatment of TBDs is complex and further complicated by the fact that these conditions may occur as the result of various bacterial, viral, or parasitic infections or even allergic responses that can affect multiple body systems with potential long-term impacts on patient health. Unfortunately, TBDs frequently go undiagnosed or misdiagnosed and as a result, the true rates of infection and burdens of the disease are unknown. Furthermore, as tick populations increase and geographically expand, it is anticipated that new pathogens and conditions/illnesses associated with tick-bites will emerge[2] and TBD incidence will continue to rise.

Continued research efforts are necessary to elucidate the mechanisms of tick-borne pathogen transmission, the human immune response to pathogens and pathogen immune evasion, the establishment of persistent infections and chronic clinical manifestations of disease, and the implications of co-infections on all of these complex processes. A need still exists for new and improved tick bite and TBD prevention strategies, as well as tick- and rodent-targeted infection prevention and control interventions. For those who are bitten, sensitive and specific assays for direct pathogen detection are vitally important, as they would ideally allow for tailored and rapidly initiated treatment plans for patients suffering acute infection, to prevent the progression toward persistent infection and symptoms. The TBDRP intends to support impactful research focused on addressing critical gaps in TBD diagnosis, treatment pathogenesis, and prevention in order to bring solutions to the U.S. military, their beneficiaries, and the American public.



FY16-FY20 TBDRP Portfolio Investment by Research Area (Number of Awards)



FY16-FY20 TBDRP Portfolio Investment by Pathogen Type (Number of Awards)

**Involves more than one or has broad applicability to multiple TBDs*

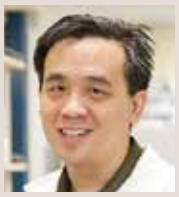
2020 Congressional Appropriations, Research Investment, and Withholds and Management Costs

Congressional Appropriations	Research Investment	Withholds and Management Costs
$7M	Career Development Award.....$879,099 Idea Development Award.....$4,896,008 Modifications to ongoing awards.....$437,338	USAMRDC .....$135,300 SBIR/STTR .....$235,000 Mgt Costs (6.29%).....$417,255
Total: $7M	**Total:** $6,212,445	**Total:** $787,555

[1] Tick-Borne Disease Working Group, 2018 Report to Congress, Chapter 1, p.5 (https://www.hhs.gov/sites/default/files/tbdwg-report-to-congress-2018.pdf).
[2] https://www.cdc.gov/media/dpk/diseases-and-conditions/lyme-disease/index.html.

MILITARY RELEVANCE

- ***Approximately 6,000 active-duty Service Members and nearly 56,000 Service Member beneficiaries were diagnosed with a reportable TBD between 2006 and 2020.***
- ***Lyme disease accounts for approximately 80% of TBDs diagnosed in Service Members and their beneficiaries.***[3]



Pathogen-Host Molecular Biosignature Lyme Disease Diagnostic Assay

Charles Chiu, M.D., Ph.D., University of California San Diego

Researchers are working to develop a Lyme disease diagnostic assay capable of accurately differentiating acute Lyme disease from other acute illnesses that may present with similar symptoms, such as influenza or sepsis. Genes that are differentially expressed in acute Lyme disease patients, as compared to non-Lyme and healthy controls, were identified, leading to the discovery of a Lyme disease-specific biomarker signature. Using machine learning analysis of this signature, a predictive model was developed for distinguishing blood samples of acute Lyme disease patients from healthy patients or those suffering from other acute illnesses. The ability to diagnose Lyme disease at all stages of infection using a non-invasive, specific, sensitive, rapid assay would improve overall patient care and result in prompt treatment that could mitigate disease progression and limit severity.

Warfighter Adaptive Barrier Controlled-Release Device (AB-CRD) for Active Protection Against Ticks

Noel Elman, Ph.D., GearJump Technologies, LLC

Current TBD prevention strategies for Service Members in the field rely on permethrin treatment of uniforms, which wanes over time, and/or frequent application of tick repellent, which may be impractical. Researchers are developing an AB-CRD that uses micro-electro-mechanical systems technology to provide controlled and sustained release of a low toxicity tick spatial repellent. The design includes remote wireless control and programming and allows for receipt of device updates. Because it is compact, the AB-CRD can be worn by the Soldier or affixed to mobile infrastructure, providing an additional line of defense against tick bites, thus reducing TBD incidence.

Monica White - Patient, Mother, and Wife Living with Lyme

Monica White has spent the past 15 years caring for herself, her two children, and her husband, all of whom are infected with Lyme disease and multiple other TBDs. In their search for care, Monica and her family met roadblocks, including misdiagnosis, denied coverage, and restricted access to Lyme disease testing. Through her own experiences and advocacy work, Monica developed a thorough understanding of the challenges faced by those suffering from TBDs: limitations in or lack of diagnostic assays, lack of treatments, the need for expanded research, and the physical, emotional, psychological, financial, and social devastation that patients and their families experience. As a TBDRP Programmatic Panel member, Monica is committed to helping to fund the best research to combat Lyme and other TBDs, bringing hope to patients and caregivers.

"What cohort of the American public is exposed to more global tick-borne illnesses than our Service Members and military families? After being medically retired from a career as a fighter pilot due to 'chronic systemic tick-borne illness,' I needed a new mission. The TBDRP allows me to be a part of the solution by sharing my own experience and helping to advance the science as a consumer peer reviewer. The patient-centered approach of the CDMRP is unique among federal funding agencies, and the TBDRP ensures that the voices of tick-borne illness patients are heard. This program gives me hope for bridging the gap between basic research and urgent patient needs."

Col Nicole Malachowski (U.S. Air Force, retired) Former F-15E Fighter Pilot, The Dean Center for Tick Borne Illness, FY16-FY20 Consumer Peer Reviewer

[3] Data from the Armed Forces Health Surveillance Branch for the years 2006-2020.

TRAUMATIC BRAIN INJURY AND PSYCHOLOGICAL HEALTH RESEARCH PROGRAM

Vision: Optimize psychological health and reduce or eliminate the effects of traumatic brain injury and traumatic stress

Mission: Fund research to understand, prevent, and treat traumatic brain injury and psychological health conditions that accelerates solutions to improve the health, well-being, and healthcare of Service Members, DOD beneficiaries, Veterans, and the American public

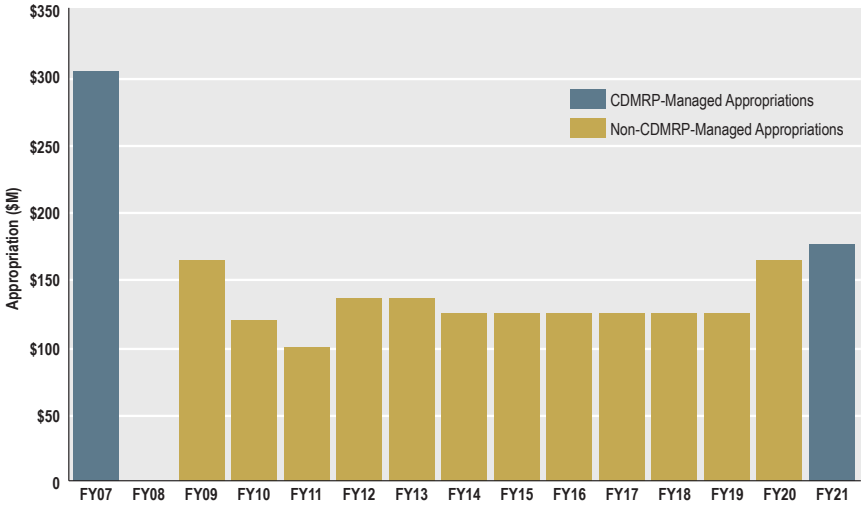
PROGRAM HISTORY

Congress appropriated funds for TBI and psychological health medical research in FY07 in response to the devastating psychological health issues and TBIs sustained by U.S. Service Members in Iraq and Afghanistan. The CDMRP managed the FY07 appropriations as the Psychological Health and Traumatic Brain Injury Research Program (PH/TBIRP). There was no appropriation for PH/TBIRP in FY08. During FY09–FY20, PH/TBIRP appropriations were managed primarily by the Joint Program Committees as directed by the Office of the Assistant Secretary of Defense for Health Affairs and the Defense Health Agency. CDMRP provided program and award management support as requested during this time. In FY21, the CDMRP is managing the appropriation as the Peer Reviewed Traumatic Brain Injury and Psychological Health Research Program (TBIPHRP). The current TBIPHRP complements and supports ongoing DOD efforts toward promoting a better standard of care for psychological health and TBI in the areas of prevention, detection, diagnosis, treatment, and rehabilitation.

FY21 TBIPHRP DEVELOPMENTS

The FY21 TBIPHRP held a stakeholders meeting to identify gaps in research and Topic Areas that aligned with the congressional language. Over 100 stakeholders from across the DOD, other federal agencies, academia, industry, and private organizations attended the meeting, which provided an open-dialogue forum for researchers, clinicians, program managers, and lived-experience subject matter experts. The outcomes from this meeting informed the programmatic discussions held during FY21 TBIPHRP Vision Setting.

At the FY21 TBIPHRP Vision Setting meeting, the Programmatic Panel members considered the program's congressional language, the research landscape, and outcomes from the FY21 Stakeholders Meeting to create the FY21 TBIPHRP Vision, Mission, and Focus Areas and to develop an investment strategy for FY21 funds.



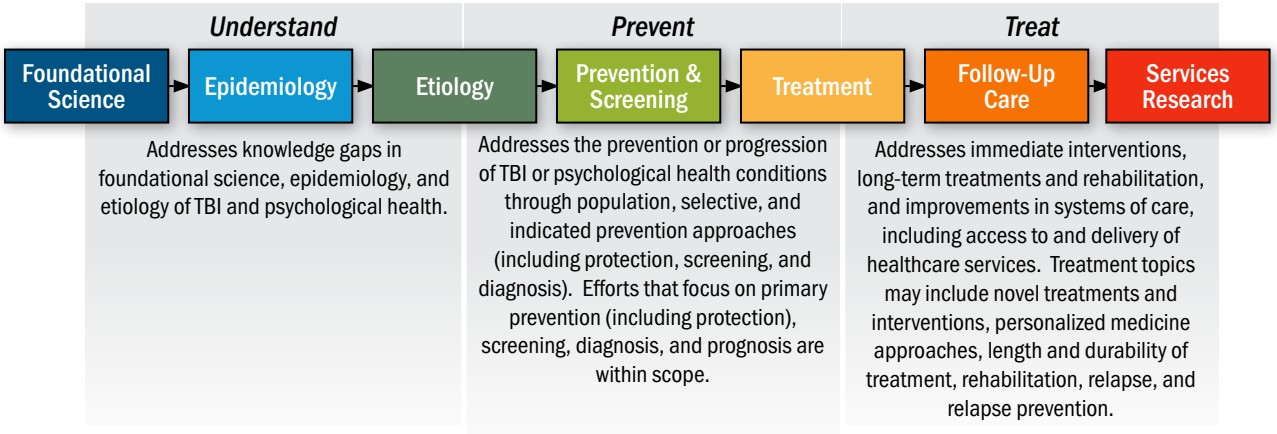
Congressional Appropriations for TBI and Psychological Health Research, CDMRP-Managed Appropriations in Dark Blue (FY07 and FY21).

"Over the years, I have had the privilege of watching the CDMRP grow, develop, and transform its mission and vison to improve the lives of others. The opportunity to contribute and engage with an interdisciplinary team of dedicated professionals as they continually strive to overcome the challenges associated with TBI has been rewarding. It is an honor to be part of this (TBIPHRP) team as we find ourselves at the forefront of supporting survivors, caregivers, and their families as they navigate the path of recovery from TBI."

CPT Charles "Char" Gatlin (U.S. Army, retired), FY21 Programmatic Panel Member

NEW FOR FY21: Enabling whole-person TBI and psychological health research, supporting engagement of scientists and community stakeholders in research, and creating opportunities for early-career investigators

FY21 TBIPHRP Research Continuum: The FY21 TBIPHRP Research Continuum provides a framework for strategic planning and evaluation of research development. Understand, Prevent, and Treat are the overarching categories used in funding opportunities to organize the FY21 TBIPHRP Focus Areas along the Research Continuum.



FY21 TBIPHRP AWARD MECHANISMS

FY21 TBIPHRP funding mechanisms support early idea development through to clinical implementation and team science.

HIGHLIGHTS FROM FY20:

Leveraging a Strong Foundation for TBIPHRP

- **Dr. Shelley MacDermid Wadsworth** (Purdue University) is studying the long-term consequences of deployed parents on children, and partnering with a large-scale prevention program for military families (FOCUS).
- **Dr. Lindsay Orchowski** (Rhode Island Hospital) is working to adapt a computerized civilian sexual assault prevention program, +Change, to prevent sexual assault among male and female Service Members.
- **Dr. Matthew Rosen** (Harvard University/Massachusetts General Hospital) developed a new, FDA-cleared, portable MRI device, the Hyperfine Swoop,™ which can operate outside of conventional imaging facilities and hospitals, moving diagnostic neuroimaging capabilities closer to the point of injury.

Maximizing the Impact of Clinical Research Data

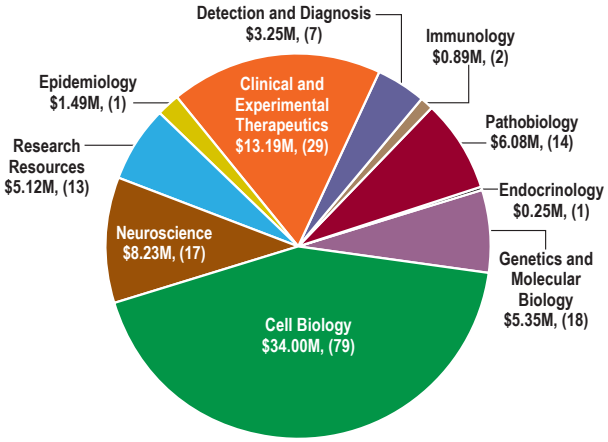
Federal Interagency TBI Research Repository (FITBIR): FITBIR is a collaboration by the DOD and the National Institute of Neurological Diseases and Stroke. FITBIR stores de-identified (no linkages to the person) human subject research data from NIH-, VA-, and DOD-funded research projects. The CDMRP is managing seven awards from the FY19 PH/TBI FITBIR Analysis Award. These awards are analyzing FITBIR data to uncover new insights in the diagnosis, management, and treatment of TBI. Below are a few examples:

- **Dr. Amy Jak** (Veterans Medical Research Foundation of San Diego) is determining how concussion outcomes differ between males and females.
- **Dr. Nicholas Port** (Indiana University) is applying analytic techniques to FITBIR data in order to predict long-term outcomes of mTBI.
- **Dr. Yvonne Liu** (New York University) is working to identify definitive imaging biomarkers of mTBI.

TUBEROUS SCLEROSIS COMPLEX RESEARCH PROGRAM

Vision: Improve prevention strategies and treatments to lessen the impact of TSC while striving for a cure

Mission: Support innovative and high-impact research that promotes discoveries in TSC, from mechanistic insights to clinical application across all ages, by fostering new ideas and investigators for the benefit of Service Members, their beneficiaries, and the American public



FY02-FY20 Portfolio Investment by SCS Code (Number of Awards)

PROGRAM HISTORY

In FY02, a congressional appropriation of $1M established the Peer Reviewed Tuberous Sclerosis Complex Research Program (TSCRP). Since then, a total of $97M has been appropriated to the program, including $8M in FY21. From FY02 to FY20, the TSCRP has funded 181 awards. Today, the TSCRP is the second largest government funding source for Tuberous Sclerosis Complex (TSC) research research in the United States.

Since its inception 19 years ago, the TSCRP has played a critical role in helping accelerate high-impact research, exploring new concepts, encouraging innovation, and bringing new investigators into the TSC field.

TSC is a rare genetic disorder that affects 25,000-50,000 individuals in the United States and 1 to 2 million individuals worldwide. The disorder is caused by mutations in either TSC1 gene or TSC2 gene, which encode the proteins hamartin and tuberin, respectively. The mutations result in hyperactivation of the mTOR pathway and cause non-malignant tumors in multiple organs, such as brain, eyes, heart, kidneys, skin, and lungs. The clinical manifestations are very broad, with the most severe being seizures, developmental delays, autism, and behavioral problems. There is no cure for TSC.

PROGRAM FOCUS AREAS

Under the guidance of the TSCRP Strategic Plan, the program identified the following Focus Areas for each of the goals:

Strategic Goals	Focus Areas
Tumor Eradication	Eradicating tumors associated with TSC and TSC-associated lymphangioleiomyomatosis (LAM), including gaining a deeper mechanistic understanding of TSC signaling pathways
Epilepsy	Preventing epilepsy, improving treatment, and mitigating comorbidities associated with TSC-related seizures
Neurodevelopmental Features	Understanding the features of TSC-associated neuropsychiatric disorders and reducing their impact, including pharmacological and behavioral interventions

2020 Congressional Appropriations, Research Investment, and Withholds and Management Costs

Congressional Appropriations	Research Investment	Withholds and Management Costs
$6M	Clinical Translational Research Award - Correlative Study..... $859,380 Exploration - Hypothesis Development Award .....$1,509,642 Idea Development Award .....$2,939,870 Modifications to ongoing awards..... $97,173	USAMRDC ..... $115,980 SBIR/STTR ..... $201,000 Mgt Costs (4.87%) $276,955
Total: $6M	**Total:** $5,406,065	**Total:** $593,935

Kate Barbato describes her experience with the TSCRP as "amazing and eye-opening… to hopefully help individuals like me far into the future! …The entire process made me feel so proud and excited to be able to really represent and give back to the community of individuals like me who are affected by TSC every day. Reading the proposals was a humbling experience, to see how many researchers are interested and care about making a difference for our community!"

Kate Barbato, Tuberous Sclerosis Alliance, FY20-FY21 Consumer Peer Reviewer

IN THE PIPELINE: FY20 AWARDS

Clinical Translational Research Award

Tumor Eradication

LAM Pilot Study with Nilotinib LAMP-2
Jeanine D'Armiento M.D., Ph.D., Columbia University Medical Center
Although inhibition of the mTOR complexes, via sirolimus, exerts cytostatic effects on tumor cells, the treatment is transient and not curative, causing recurrence of tumors upon cessation of therapy. This reveals the need to identify mTOR-independent pathologic mechanisms that can account for the timing of onset and growth of tumors in TSC patients. This project will establish the tolerability of nilotinib (an FDA-approved drug for leukemia that initiates LAM cell death) in patients with LAM both on and off sirolimus therapy.

Idea Development Award

Tumor Eradication

Mechanistic Understanding of m6A Signaling for the Treatment of TSC and LAM
Gina Lee, Ph.D., University of California Irvine

Neurodevelopmental Features

Developing a Novel Therapy for Neurological Symptoms of Tuberous Sclerosis Complex
Dr. Akira Yoshii, M.D., Ph.D., University of Illinois at Chicago

Preventing Epilepsy | Neurodevelopmental Features

The Contribution of Rapamycin-Insensitive Processes to Neurological Symptoms in TSC
Mustafa Sahin, M.D., Ph.D., Boston Children's Hospital

Preventing Epilepsy

Mechanisms of Epileptogenesis and Circuit Dysfunction in a Mouse Model of TSC
Anne Anderson, M.D., Baylor College of Medicine

Exploration – Hypothesis Development Award

Preventing Epilepsy

The Role of Blood-Brain Barrier Dysfunction in Epilepsy in TSC
Michael Wong, M.D., Ph.D., Washington University

KCC2 Dysfunction Enhances Synaptic Excitability of Cytomegalic Neurons in TSC
Wudu Lado, Ph.D., Columbia University Medical Center

Dissecting Mechanisms Underlying Brain Calcification in TSC
Mark Hester, Ph.D., Research Institute at Nationwide Children's Hospital

Tumor Eradication

Therapeutic Targeting of the Immune Checkpoint Molecule B7-H3 in TSC
Heng-Jia Liu, Ph.D., Brigham and Women's Hospital

Characterization of Estrogen-mTORC1 Signaling Network in TSC/LAM
Marina Holz, Ph.D., New York Medical College

Toward Pharmacological Rescue of TSC Loss of Function
Dr. David Sabatini, M.D., Ph.D., Whitehead Institute for Biomedical Research

VISION RESEARCH PROGRAM

Vision: Transform visual system trauma care for our armed forces and the nation

Mission: To address clinical needs through innovative research targeting the mechanism, effects, and treatment of Service-connected eye injuries and vision dysfunction

PROGRAM HISTORY

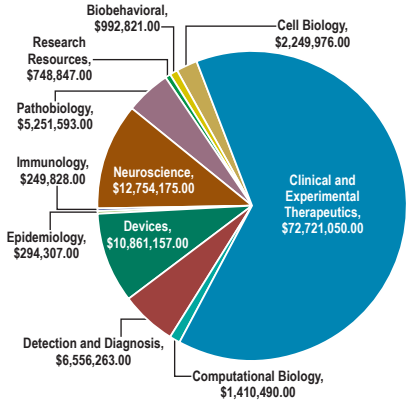
The Peer Reviewed Vision Research Program (VRP) is the leading funder of research on visual system trauma, including injuries to the ocular system and visual dysfunction associated with TBI. Congress established the VRP in 2009, and the program has received annual appropriations totaling $124.95M through FY20. Research supported by the VRP spans the continuum of care, from point-of-injury and en route care to acute definitive care to chronic care and vision restoration.

RELEVANCE TO MILITARY HEALTH

Eye injury and visual dysfunction resulting from battlefield trauma affect a large number of Service Members and Veterans. Eye injury accounts for approximately 15% of all injuries from battlefield trauma sustained during the wars in Afghanistan and Iraq. Between 2000 and 2017, the U.S. Armed Forces reported approximately 276,000 eye injury incidents, more than 6,000 of which were at high risk of blindness. In addition, through the third quarter of 2020, more than 430,000 U.S. Service Members have sustained TBI, which is associated with a broad range of visual dysfunction ranging from light sensitivity to total blindness.

FOCUS AREAS

- Eye injury or visual dysfunction as related to a military-relevant traumatic event. Examples of military-relevant trauma may include, but are not limited to:
  - Blast, penetrating, blunt, thermal, or chemical trauma
  - Trauma caused by directed energy weapons such as laser, high-power microwaves, and particle beams
- Diagnosis, stabilization, and treatment of eye injuries in austere environments and prolonged field care settings
- Restoration of visual function after trauma-related vision loss or severe visual impairment



FY09-FY20 VRP Portfolio Investment by SCS Code

2020 Congressional Appropriations, Research Investment, and Withholds and Management Costs

Congressional Appropriations	Research Investment	Withholds and Management Costs
$20M	Investigator-Initiated Research Award ..... $11,290,276 Translational Research Award ..... $5,713,897 Modifications to ongoing awards..... $1,158,851	USAMRDC ..... $386,580 SBIR/STTR ..... $671,000 Mgt Costs (4.11%)..... $779,396
Total: $20M	**Total:** $18,163,024	**Total:** $1,836,976

CORNEAL INJURY RESEARCH IN-PROGRESS REVIEW MEETING

On March 15, 2021, more than 60 attendees from the DOD Research and Development community, ophthalmology and optometry services, other federal and non-federal funders of vision research, academia, and consumer groups gathered virtually to review progress made in corneal injury research and identify challenges remaining. Lt. Col Marcus Neuffer, M.D., a cornea specialist from the U.S. Air Force Academy, gave a talk on combat corneal complications and care. Drs. Reza Dana and Joseph Ciolino from the Schepens Eye Research Institute, Dr. Ali Djalilian from the University of Illinois at Chicago, Dr. Yiqin Du from the University of Pittsburgh, Dr. Noorjahan Panjwani from Tufts University, and Dr. Gere diZerega from U.S. Biotest, Inc., presented results and outcomes from their VRP-funded research covering a wide range of topics on corneal injury and treatment. The attendees discussed future directions of corneal injury research, pathways and hurdles to clinical translation, and special considerations for the treatment of corneal injury in austere environments.

"Being a consumer reviewer for the VRP has allowed me to gain further knowledge of a variety of research. While engaging in peer review with peers of different professional levels, it was interesting to hear each other's views of the research. The Vision Research Program has the capability to promote groundbreaking research to better serve both military Service Members and civilians."

Monica Gilmore, Blinded Veterans Association, FY15, FY17-FY18, FY20 Consumer Peer Reviewer

HOT OFF THE PRESS FROM VRP-FUNDED RESEARCH

Qian R, et al. 2021. In Vivo Quantitative Analysis of Anterior Chamber White Blood Cell Mixture Composition Using Spectroscopic Optical Coherence Tomography. *Biomed Opt Express*. Mar 17;12(4):2134-2148.

Anterior uveitis is the most common form of intraocular inflammation. Currently, understanding the cell types involved in anterior uveitis relies on an invasive procedure to obtain fluid from the anterior chamber for cell composition analysis. **Dr. Joseph A. Izatt** and team at **Duke University** developed a noninvasive imaging-based method to estimate the composition of cell type mixture and validated the accuracy of the estimation in vitro and in vivo. **This work is a promising advancement toward noninvasive quantitative diagnosis of cellular responses in the uveitis patients in the clinic.**

Jmaeff S, et al. 2020. Small-Molecule Ligands That Bind the RET Receptor Activate Neuroprotective Signals Independent of but Modulated by Coreceptor GFRa1. *Mol Pharmacol.* Jul;98(1):1-12.

The growth factor glial cell line-derived neurotrophic factor (GDNF) binds a GDNF family receptor alpha-1 (GFRα1) receptor, and the complex activates the tyrosine kinase receptor RET. Activated RET promotes survival signals in neuronal cells. **Dr. H. Uri Saragovi** and team at **McGill University** screened a chemical library to identify a novel class of small molecules that bind to and activate RET in the absence of GFRα1 or GDNF. The lead molecule significantly reduces neuronal death in a mouse model of retinitis pigmentosa, **demonstrating potential as a monotherapy for neurodegeneration after eye injury or diseases.**

Halász É, et al. 2021. ROCK Inhibition Reduces Morphological and Functional Damage to Rod Synapses After Retinal Injury. *Sci Rep*. Jan 12;11(1):692.

Synaptic disjunction after retinal detachment negatively impacts visual recovery after retinal reattachment surgery. **Dr. Ellen Townes-Anderson** and team at **Rutgers University** investigated the time course and histopathology of synaptic disjunction in a pig model of retinal detachment. They demonstrated that a small-molecule inhibitor of the Rho-kinase ROCK significantly reduced synaptic damage and improved function of rod photoreceptors. Stabilization of synaptic circuitry by ROCK inhibition offers **a potential therapy for retinal detachment and other CNS trauma and diseases.**

Weng L, et al. 2020. The Anti-Scarring Effect of Corneal Stromal Stem Cell Therapy Is Mediated by Transforming Growth Factor β3. *Eye Vis (Lond).* Nov 3;7(1):52.

Corneal scarring is a major cause of blindness in patients of ocular trauma or infection. **Dr. Yiqin Du** and team at the **University of Pittsburgh** showed that corneal stromal stem cells (CSSC), when transplanted to wounded mouse corneas, prevented scarring. The team further discovered that the anti-scarring effect of CSSC is at least partially dependent on their production and secretion of transforming growth factor β3. **CSSC is a promising agent in the regeneration of unscarred stroma in corneal injury patients.**

Lee IK, et al. 2021. Ultrathin Micromolded 3D Scaffolds for High-Density Photoreceptor Layer Reconstruction. *Sci Adv.* Apr 21;7(17):eabf0344.

Polymer scaffolds, a technology with wide applications in tissue engineering and regeneration, have successfully delivered retinal pigment epithelium monolayer to patients of age-related macular degeneration. To help patients with severe photoreceptor degeneration, a multidisciplinary team led by **Drs. Zhenqiang Ma, Shaoqin Gong, and David Gamm** at the **University of Wisconsin, Madison**, fabricated and optimized a biodegradable scaffold with unique structures to support the seeding, organization, and polarization of high-density photoreceptors. **This novel scaffold holds the promise of superior photoreceptor survival and function after transplantation.**

APPENDIX A: FY20-FY21

Table A-1. CDMRP Programs, Appropriations, and Applications Received and Awarded in FY20-FY21

Research Programs Managed by the CDMRP	FY20				FY21	
	Funds Received (in millions)	Applications Received	Applications Funded	Funding Modifications Completed	Funds Received (in millions)	Applications Received to Date
Alcohol and Substance Abuse Disorders	0				$4	5
Amyotrophic Lateral Sclerosis	$20	87	24	6	$40	90
Autism	$15	96	12	1	$15	89
Bone Marrow Failure	$3	26	5		$7.5	
Breast Cancer	$150	1,505	94	5	$150	1,294
Breast Cancer Research Semipostal[1]	$0.5		1		$0.5	
Chronic Pain Management	$15	86	10		$15	
Combat Readiness Medical Research	$10	61	5		$10	
Duchenne Muscular Dystrophy	$10	63	14		$10	
Epilepsy	$12	44	9		$12	39
Gulf War Illness	$22	40	23	11	$22	61
Hearing Restoration	$10	47	12		$10	
Joint Warfighter Medical[2]	$40	46	11	2	$40	87
Kidney Cancer	$40	234	56	5	$50	78
Lung Cancer	$14	359	27	1	$20	392
Lupus	$10	69	10	1	$10	68
Melanoma	$20	187	32		$30	72
Military Burn	$10	17	6	1	$10	
Multiple Sclerosis	$16	97	20		$20	
Neurofibromatosis	$15	86	21	1	$20	70
Neurotoxin Exposure Treatment Parkinson's	$16	76	14		$16	37
Orthotics and Prosthetics Outcomes	$15	54	14		$15	35
Ovarian Cancer	$35	233	47		$35	261
Pancreatic Cancer	$6	76	9		$15	
Peer Reviewed Alzheimer's	$15	55	10	1	$15	59
Peer Reviewed Cancer[3]	$110	622	98	2	$115	591
Peer Reviewed Medical[4]	$360	1,940	200	9	$370	1,335
Peer Reviewed Orthopaedic	$30	92	20	15	$30	82
Prostate Cancer	$110	583	102	11	$110	475
Rare Cancers	$7.5	378	18		$17.5	114
Reconstructive Transplant	$12	55	13	5	$12	
Scleroderma	$5	52	10		$5	39
Spinal Cord Injury	$40	152	24	1	$40	176
Tick-Borne Disease	$7	39	7	2	$7	45
Traumatic Brain Injury and Psychological Health	n/a				$175	
Tuberous Sclerosis	$6	44	11		$8	59
Vision	$20	85	17	2	$20	
Total	**$1,227.0**	**7,686**	**1,006**	**82**	**$1,501.5**	**5,653**

[1] Breast Cancer Semipostal funds applications received and reviewed by the BCRP

[2] Joint Warfighter Medical Execution Management Breakdown: 11 awards and 2 mods managed by the CDMRP; 1 mods managed by USAMMDA; and 1 mod managed by Navy Sea Warrior Office

[3] FY21 Peer Reviewed Cancer Research Program: The agreement provides $115M for a peer-reviewed cancer research program to research cancers not addressed in the breast, prostate, ovarian, and lung cancer research programs currently executed by the Department of Defense. The funds provided in the Peer Reviewed Cancer Research Program are directed to be used to conduct research in the following areas: beryllium, bladder cancer, blood cancers, brain cancer, colorectal cancer, endometrial cancer, esophageal cancer, germ cell cancer, head and neck cancer, liver cancer, lymphoma, mesothelioma, metastatic cancer, neuroblastoma, pediatric brain tumors, pediatric, adolescent, and young adult cancers, sarcoma, stomach cancer, thyroid cancer, link between scleroderma and cancer.

[4] FY21 Peer Reviewed Medical Research Program: The agreement provides $370M for a peer-reviewed medical research program. The Secretary of Defense, in conjunction with the Service Surgeons General, is directed to select medical research projects of clear scientific merit and direct relevance to military health. Research areas considered under this funding are restricted to the following areas: arthritis, burn pit exposure, cardiomyopathy, congenital heart disease, diabetes, dystonia, eating disorders, emerging viral diseases, endometriosis, epidermolusis bullosa, familial hypercholesterolemia, fibrous dysplasia, focal segmental glomerulosclerosis, food allergies, Fragile X syndrome, frontotemporal degeneration, hemorrhage control, hepatitis B, hydrocephalus, hypertension, inflammatory bowel disease, malaria, metals toxicology, mitochondrial disease, myalgic encephalomyelitis/chronic fatigue syndrome, myotonic dystrophy, non-opioid therapy for pain management, nutrition optimization, pathogen-inactivated blood products, peripheral neuropathy, plant-based vaccines, platelet-like cell production, polycystic kidney disease, pressure ulcers, pulmonary fibrosis, respiratory health, rheumatoid arthritis, sleep disorders and restriction, suicide prevention, sustained-release drug delivery, vascular malformations, and women's heart disease.

APPENDIX B: ACRONYMS

3D ..... Three-Dimensional
AA ..... Aplastic Anemia
AB-CRD ..... Adaptive Barrier Controlled-Release Device
ACERT..... Adaptive Catalysis of ConvErgent Research Training
ACS ..... American Cancer Society
AD .....Alzheimer's Disease
ADRD.....Alzheimer's Disease-Related Dementias
ALI ..... Acute Lung Injury
ALS ..... Amyotrophic Lateral Sclerosis
ALSRP.....Amyotrophic Lateral Sclerosis Research Program
AMPK..... AMP-Activated Protein Kinase
AO .....Antisense Oligonucleotide
AOPA ..... American Orthotic and Prosthetic Association
ARDS.....Acute Respiratory Distress Syndrome
ARP .....Autism Research Program
ASADRP..... Peer Reviewed Alcohol and Substance Abuse Disorders Research Program
ASD ..... Autism Spectrum Disorder
ASUD.....Alcohol Substance Use Disorders
AUD .....Alcohol Use Disorder
AYA .....Adolescent and Young Adult
B ..... Billion
BCI ..... Brain-Computer Interface
BCRP ..... Peer Reviewed Breast Cancer Research Program
BGA.....Blood Group Antibody
BMF.....Bone Marrow Failure
BMFRP..... Bone Marrow Failure Research Program
BXCL501 ..... Dexmedetomidine HCl
CARE .....Concussion Assessment, Research, and Education Consortium
ccRCC..... Clear Cell Renal Cell Carcinoma
CDA .....Clinical Development Award
CDMRP ..... Congressionally Directed Medical Research Programs
CNS .....Central Nervous System
CPMRP .....Chronic Pain Management Research Program
CRRP .....Combat Readiness – Medical Research Program
CSSC..... Corneal Stromal Stem Cells
CSVCC ..... Convergent Science Virtual Cancer Center
CT.....Computed Tomography
DBA.....Diamond Blackfan Anemia
DHA..... Defense Health Agency
DLS ..... Daily Living Skills
DMD .....Duchenne Muscular Dystrophy
DMDRP..... Duchenne Muscular Dystrophy Research Program
DMSS ..... Defense Medical Surveillance System
DOD .....Department of Defense
eADAPT-HP .....Enhanced Auto-Diagnostic Adaptive Precision Training for Myoelectric Prosthesis
EBLens .....EyeBOX Lens
ECHO .....Extension for Community Healthcare Outcomes
EMT .....Mesenchymal Transition
ERP .....Epilepsy Research Program
FDA.....Food and Drug Administration
FEN..... Fentanyl
FITBIR .....Federal Interagency TBI Research Repository
FMD.....Fasting-Mimicking Diets
FUS-ASO.....Fused in Sarcoma-Antisense-Oligonucleotide
FY..... Fiscal Year
GAO.....Government Accountability Office
GDNF.....Glial Cell Line-Derived Neurotrophic Factor
GFRα1 ..... GDNF Family Receptor Alpha-1
GI .....Gastrointestinal
GWI .....Gulf War Illness
GWI SOTS ..... Gulf War Illness State of the Science
GWRIP ..... Gulf War Illness Research Program
HER2 .....Human Epidermal Growth Factor Receptor 2
HGSC..... High-Grade Serous Ovarian Cancer
HIIT.....High Intensity Interval Training
HOBSCOTCH .....HOme-Based Self-management and COgnitive Training Changes Lives
HR+ .....Hormone Receptor Positive
HRRP ..... Hearing Restoration Research Program
ICB .....Immune Checkpoint Blockage
IDA ..... Idea Development Award
ILD.....Interstitial Lung Disease
IND ..... Investigational New Drug
iTregs..... Induced Regulatory T Cells
JPC .....Joint Program Committees
jSSc.....Juvenile-Onset Systemic Sclerosis
JWMRP ..... Joint Warfighter Medical Research Program
KCRP .....Kidney Cancer Research Program
LAM.....Lymphangioleiomyomatosis
LCRP.....Lung Cancer Research Program
LFA .....Lupus Foundation of America
LGG ..... Low-Grade Gliomas
LIMBIC..... "Long-Term Impact of Military-Relevant Brain Injury Consortium"

LLP ..... Lower Limb Prosthesis
LRP..... Lupus Research Program
M.....Million
M2SR ..... M2-Deficient Single Replication
MBRP ..... Military Burn Research Program
MHS .....Military Health System
MIE.....Multidisciplinary Intervention for Encopresis
MOA .....Memorandum of Agreement
MRI..... Magnetic Resonance Imaging
MRP..... Melanoma Research Program
MS..... Multiple Sclerosis
MSRP .....Multiple Sclerosis Research Program
mTBI .....Mild Traumatic Brain Injury
mTOR.....Mammalian Target of Rapamycin
NBWT ..... Narrow Beam Walking Test
NCI ..... National Cancer Institute
NETP.....Neurotoxin Exposure Treatment Parkinson's
NF .....Neurofibromatosis
NF1 ..... Neurofibromatosis Type 1
NF2 ..... Neurofibromatosis Type 2
NFCTC..... Neurofibromatosis Clinical Trials Consortium
NFRP ....Peer Reviewed Neurofibromatosis Research Program
NIH .....National Institutes of Health
NK ..... Natural Killer Cells
NLK ..... Nemo-Like Kinase
NPC ..... Nephron Progenitor Cells
NSCLC .....Non-Small Cell Lung Cancer Treatment
nTregs .....Naturally Occurring Regulatory T Cells
OCR ..... Oxygen Consumption Rates
OCRP ..... Ovarian Cancer Research Program
OEF.....Operation Enduring Freedom
OIF..... Operation Iraqi Freedom
OND ..... Operation New Dawn
OPORP.....Orthotics and Prosthetics Outcomes Research Program
ORD..... Office of Research and Development
OUD.....Opioid Use Disorder
PA..... Program Announcement
PAPD5 ..... Poly(A) Polymerase PAP-Associated Domain-Containing 5
PARP..... Poly (ADP-Ribose) Polymerase
Pca .....Prostate Cancer
PCARP .....Pancreatic Cancer Research Program
PCP ..... Primary Care Provider
PD .....Parkinson's Disease
PDR ..... Pan Drug Resistant
PET.....Positron Emission Tomography
Pfn1 .....Profiling 1
PH .....Psychological Health
PH/TBIRP ..... Psychological Health and Traumatic Brain Injury Research Program
PI..... Principal Investigator
PN ..... Plexiform Neurofibroma
POI .....Point-of-Injury
PRARP ..... Peer Reviewed Alzheimer's Research Program
PRCP ..... Prostate Cancer Research Program
PRCRP ..... Peer Reviewed Cancer Research Program
PRMRP .....Peer Reviewed Medical Research Program
PRORP .....Peer Reviewed Orthopaedic Research Program
PSA .....Prostate-Specific Antigen
PTE .....Post-Traumatic Epilepsy
PTSD ..... Post-Traumatic Stress Disorder
PUFA.....Polyunsaturated Fatty Acids
pwMS .....People with Multiple Sclerosis
R&A.....Review and Analysis
rAAV .....Recombinant Adeno-Associated Viral
RANKL .....Receptor Activator of Nuclear Factor Kappa-Ligand
RCRP ..... Rare Cancers Research Program
ROCK..... Rho-Kinase
RPS19 ..... Ribosomal Protein S19
RTRP..... Reconstructive Transplant Research Program
SBIR ..... Small Business Innovation Research
SCDRx ..... Selective Cytopheretic Device Therapy
SCI ..... Spinal Cord Injuries
SCIRP .....Spinal Cord Injury Research Program
SCS .....Scientific Classification System
SEER .....Surveillance, Epidemiology, and End Results
SLE.....Systemic Lupus Erythematosus
SRP .....Scleroderma Research Program
SSc..... Scleroderma/Systemic Sclerosis
STRW.....Surviving and Thriving in the Real World
STTR ..... Small Business Technology Transfer
SWAT .....Short Wave Assessment Tool
TBD .....Tick-Borne Disease
TBDRP ..... Tick-Borne Disease Research Program
TBI.....Traumatic Brain Injury
TBIPHRP ..... Traumatic Brain Injury and Psychological Health Research Program
TERC.....Telomerase RNA Component
TGF .....Transforming Growth Factor

TRACK-TBI.....Transforming Research and Clinical Knowledge in Traumatic Brain Injury
TSC.....Tuberous Sclerosis Complex
TSCRP.....Peer Reviewed Tuberous Sclerosis Complex Research Program
TVA.....Transformative Vision Award
UE-VCA ..... Upper Extremity Vascularized Composite Allotransplantation
USAMMDA ... US Army Medical Materiel Development Activity
USAMRAA..... US Army Medical Research Acquisition Activity
USAMRDC.....Director's Letter
USAMRDC..... US Army Medical Research and Development Command
VA..... US Department of Veterans Affairs
VCA ..... Vascularized Composite Allotransplantation
VCC .....Virtual Cancer Center
VHL..... Von-Hippel Lindau
VRP ..... Vision Research Program
WeCAN .....Wellness, Coping, and Adaptation for Neurologic Conditions
WRNMMC ..... Walter Reed National Military Medical Center
WT.....Wilms Tumor

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