Congressionally Directed Medical Research Programs

2022

Annual Report

CDMRP

DEPARTMENT OF DEFENSE

CONGRESSIONALLY DIRECTED MEDICAL RESEARCH PROGRAMS

LETTER FROM THE DIRECTOR

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

The Congressionally Directed Medical Research Programs (CDMRP) is pleased to present our 2022 Annual Report. CDMRP supports research focuses on innovative and impactful research that advances health care for our Service Members, Veterans, their families, and the American public.

The 2022 Annual Report updates stakeholders on changes to CDMRP-wide policies and practices, describes our investments within the CDMRP's 35 distinct medical research programs, and highlights important research outcomes that are advancing care and improving lives.

We remain grateful for our partners representing consumer and non-profit organizations, other 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. Their contributions to our programs' strategy and their participation throughout our two-tier review process are integral to our success.

We are honored that Congress has trusted the CDMRP for the last 30 years to transform health care through innovative and impactful research.

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, 2022

Congressionally Directed Medical
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INTRODUCTION

CDMRP's Vision: Transform health care through innovative and impactful research

CDMRP's Mission: Responsibly manage collaborative research that discovers, develops, and delivers health care solutions for Service Members, Veterans, and the American public

About This Report: This annual report describes the accomplishments and activities of the CDMRP for fiscal year 2022 (FY22) from October 2021 through September 2022. During this time, the CDMRP executed its FY21 budget ($1.50 billion [B]), obligating 100% of the appropriation received. CDMRP also conducted FY22 program activities to include holding stakeholder and vision setting meetings as well as releasing funding opportunity announcements.

CDMRP
DEPARTMENT OF DEFENSE
CONGRESSIONALLY DIRECTED MEDICAL RESEARCH PROGRAMS

THE CONGRESSIONALLY DIRECTED MEDICAL RESEARCH PROGRAMS (CDMRP) is a directorate within the U.S. Army Medical Research and Development Command (USAMRDC) that was established in 1992 when Congress added funds within the Defense Appropriations Act for breast cancer research. Since its inception 30 years ago, Congress added several additional research programs to the Defense Appropriations Bill.

In 2022, the CDMRP managed 35 FY22 Congressional Special Interest programs. The CDMRP also provided program and award management support to other core Department of Defense (DOD) medical research programs.

The CDRMP invests in groundbreaking research across the full spectrum of research and development, including basic, translational, and clinical research. By strategically funding high-risk, high-reward research projects that other agencies may not be willing to fund, the CDMRP addresses critical research gaps. CDMRP-funded research benefits not only military members, military retirees, and family members, but the civilian population as well.

APPROPRIATION HISTORY

Since FY92, CDMRP has managed more than $16 billion in Congressional Special Interest funding. For FY22, the CDMRP managed appropriations for 35 programs totaling $1.545B, a $43 million (M) increase compared to FY21. Figure 1 depicts CDMRP funding over the last five years.

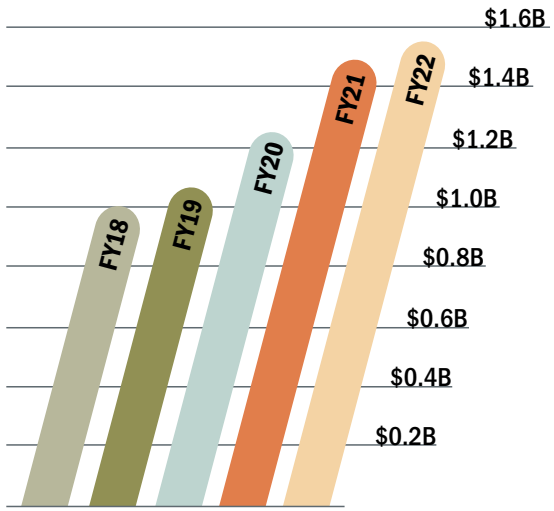
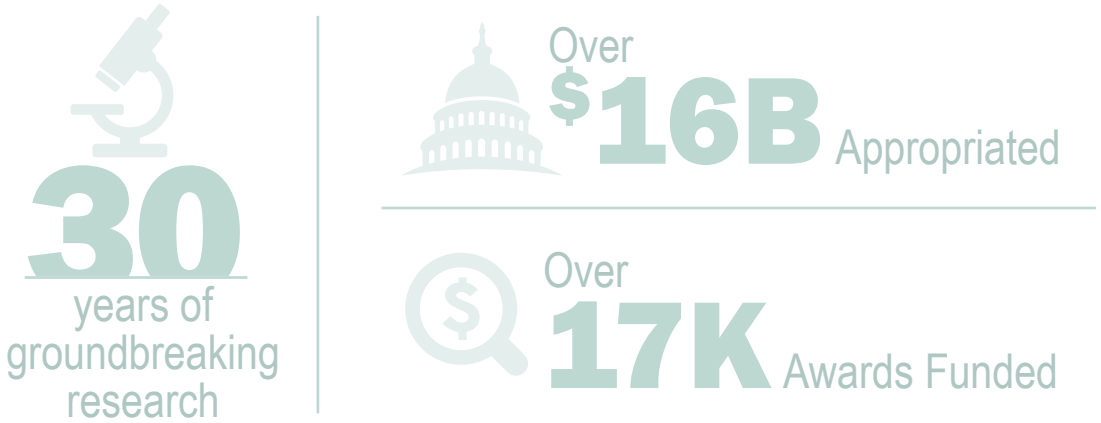


Figure 1. FY18-FY22 CDMRP Congressional Appropriations



Retired U.S. Marine Corps Col. Todd Desgrosseilliers, HRRP Programmatic Panel Member FY17-FY22

"As a combat-wounded disabled Veteran who suffers from hearing loss, vertigo, other vestibular issues, as well as tinnitus, I cannot overstate the importance of the CDMRP and its HRRP. This program provides focused research opportunities to provide innovative solutions to a disability that adversely impacts the daily activities of many Veterans and active-duty personnel. It is truly an honor and a privilege to continue to serve as an HRRP Panelist and Consumer Advocate."

STAGES OF THE CDMRP MANAGEMENT CYCLE

Under the leadership of a CDMRP Program Manager, each program follows the management cycle in Figure 2 described in detail below.

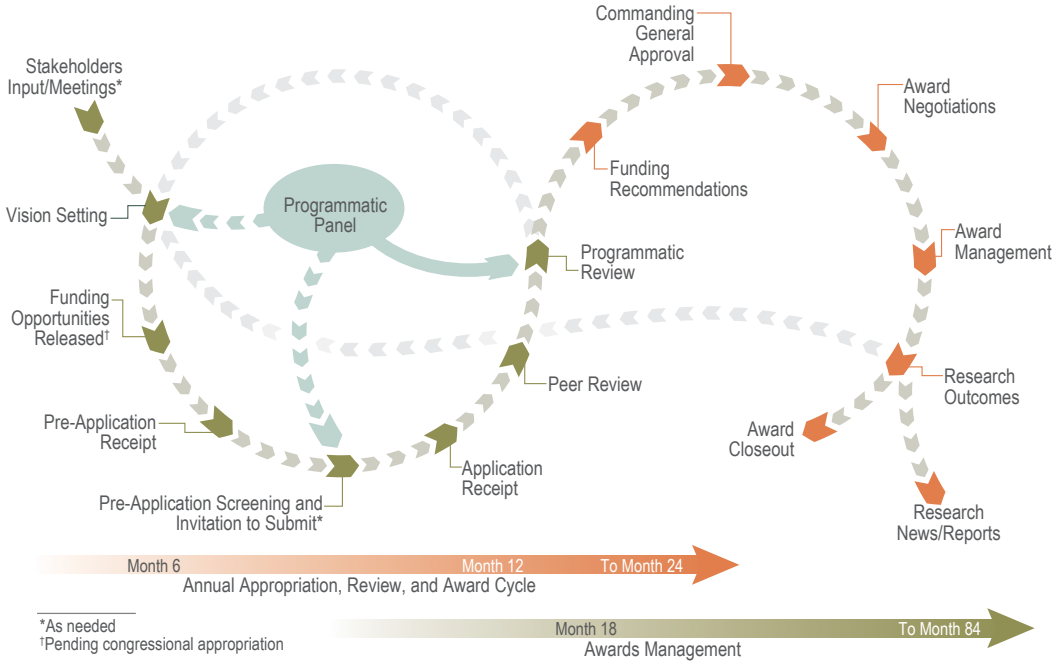


Figure 2. CDMRP Management Cycle

- **Funding Process** – CDMRP funding is not included in the DOD's annual budget request to Congress. Funding for CDMRP is specified in the Defense Appropriations Act.
- **Stakeholders Input/Meetings** – Stakeholders survey the research landscape and identify important gaps and research opportunities.
- **Vision Setting** – Programmatic Panel members discuss the state of the science, stakeholder needs, and historical areas of investment by the program as well as other funders; develop a recommended investment strategy to fill critical research gaps and meet program goals.
- **Funding Opportunity Release** – Specific fiscal year funding opportunities are made publicly available and detail programmatic intent; type of studies being requested; eligibility; submission requirements; and application review criteria.
- **Application Submission and Receipt** – Application submission consists of a two-step process requiring BOTH pre-application submission (which includes a letter of intent or a pre-proposal, as specified in the announcement) as well as full application submission. Detailed information regarding submission requirements is provided in the funding opportunity announcement.
- **Two-Tier Review Process** – Full applications undergo two tiers of review.
  - Tier I involves a peer review where each application is individually reviewed based on specific review criteria in the funding announcement to assess scientific merit. Reviewers include scientific/technical subject matter experts and consumer representatives.
  - Tier II involves Programmatic Panel members reviewing applications comparatively while considering additional programmatic factors such as adherence to the award mechanism, programmatic goals, portfolio composition, impact, and military relevance.

  More information can be found here: https://cdmrp.health.mil/about/2tierRevProcess
- **Funding Approval** – The Commanding General of the USAMRDC is the approval authority for all CDMRP awards recommended for funding.
- **Award Management** – CDMRP monitors awards for technical progress and compliance with award terms and conditions throughout their entire period of performance.

PROGRAM UPDATES

- The new **Toxic Exposures Research Program** (TERP) received a $30M appropriation in FY22 to cover a broad range of research topics, including neurotoxin exposure, Gulf War Illness, airborne hazards and burn pits, as well as other military service-related toxic exposures, including prophylactic medications, pesticides, organophosphates, toxic industrial chemicals, materials, metals, and minerals.
- The **Gulf War Illness Research Program** (GWIRP) did not receive an appropriation for FY22. Program staff will continue to manage ongoing open GWIRP awards and are coordinating closely with the new TERP, which also includes a focus on Gulf War Illness.
- For FY22, Congress transitioned the **Neurotoxin Exposure Treatment Parkinson's** (NETP) program to the **Parkinson's Research Program** (PRP), broadening the program's research focus.
- For FY22, the **Alcohol and Substance Abuse Disorder Research Program** underwent a name change to the **Alcohol and Substance Use Disorder Research Program** (ASUDRP) to align with congressional language and to reflect updated language in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition and language used by other federal agencies.
- The FY22 **Peer Reviewed Medical Research Program** (PRMRP) appropriation included 50 research topics, eight more topics as compared to FY21.
- Finally, the **Scleroderma Research Program** (SRP) did not receive an appropriation for FY22, but program staff continue to manage the 21 awards funded through the FY20 and FY21 appropriations.

FY22 Program Appropriation Changes

CDMRP Program	FY21 $M	FY22 $M	Change in $M
Melanoma	30	40	10
Orthotics and Prosthetics Outcomes	15	20	5
Ovarian Cancer	35	45	10
Peer Reviewed Cancer	115	130	15
Toxic Exposures Research Program	0	30	30
Gulf War Illness Research Program	22	0	-22
Neurotoxin Exposure Treatment Parkinson's	16	0	-16
Parkinson's	0	16	16
Scleroderma	5	0	-5

U.S. GOVERNMENT ACCOUNTABILITY OFFICE (GAO) REVIEWS

The CDMRP underwent a comprehensive review by the Comptroller General, as directed in the FY21 Defense Appropriations Act (HR 133). **The GAO favorably assessed the CDMRP and provided entirely positive findings, listing no deficiencies and providing no recommendations for change (https://www.gao.gov/assets/gao-22-105107.pdf).** The GAO analyzed budget data from the CDMRP's programs for fiscal years 2015 through 2019 and found that the DOD obligated nearly 100% of its CDMRP appropriations.

The report noted that the CDMRP supports biomedical research investments through **effective program and project management**. The CDMRP award cycle, which establishes mid- to long-term priorities by developing strategic plans and short-term priorities through annual vision setting, ensures that investments are aligned with program goals and visions.

The GAO indicated that the **CDMRP coordinates effectively with other federal agencies**, including the NIH and VA, on program planning, project selection, and identification of potential research overlap. **The GAO staff also commended the CDMRP website for transparency and the amount of publicly available information provided on programs and funding**.

CDMRP also participated in six additional GAO engagements in FY22, including a Regenerative Medicine Technology Assessment and reviews of:

- Diversity in Federally Funded Cancer Clinical Trials
- Federal Funding for U.S.-China Research Collaborations
- Federal Research Contributions to Drug Development
- U.S. Support to High-Risk Biological Research in Other Countries
- Dietary Guidelines for Americans

UPDATES TO CDMRP POLICY ON INCLUSION OF WOMEN AND MINORITIES IN CLINICAL RESEARCH

In FY21, the CDMRP issued new policy and guidelines 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." As part of this policy, all clinical research funded by CDMRP must provide anticipated enrollment table(s) for the inclusion of women and minorities at time of application as well as updated inclusion enrollment reports throughout the life of the award.

In FY22, CDMRP worked together with the DOD and NIH to obtain Office of Management and Budget approval for a new Public Health Service Inclusion Enrollment Report form and subsequent approval of the DOD's Request for Common Form. This effort allows the DOD, including CDMRP, to use the same form as the NIH to collect enrollment information on the basis of sex/gender, race, and/or ethnicity, streamlining and standardizing the reporting process across these federal agencies.[1]

[1] 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.

CONSUMER PARTNERSHIP

A CDMRP hallmark is the inclusion of consumers in vision setting meetings, 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 important perspective and insight on the needs of the affected community and bring a sense of urgency to the entire process. Throughout the CDMRP's 30 years, consumers have served alongside scientists, clinicians, and leading experts with an equal voice and vote in deliberations and strategic planning.

During FY22

71 consumers served on programmatic panels to help develop program investment strategies and make funding recommendations

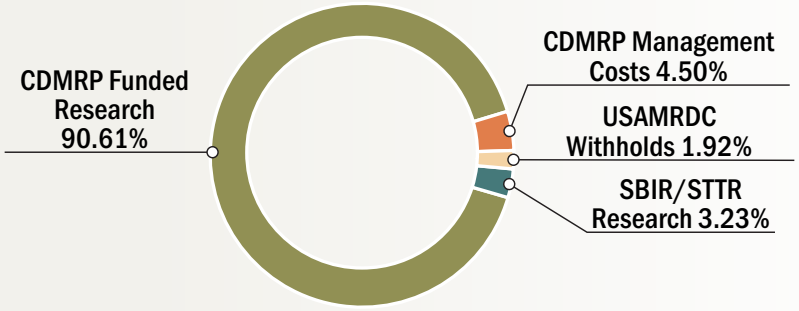
737 consumers served on CDMRP peer review panels to help evaluate the potential impact of proposed research on affected communities

4,599 consumers have represented their communities and organizations at least once since CDMRP's inception in 1992

CONGRESSIONAL APPROPRIATIONS BREAKDOWN

CDMRP strives to maximize the amount of funding that goes toward scientific research. For the FY21 appropriation, over 90% of the $1.50B directly supported innovative and impactful research. The rest was divided among CDMRP research management costs and required administrative withholds for the U.S. Army Medical Research & Development Command (USAMRDC) and the Small Business Innovation Research/Small Business Technology Transfer (SBIR/STTR) program. Funding withheld for SBIR/STTR is used to support research through the SBIR and STTR programs.

By implementing effective project and program management processes, CDMRP is able to keep its research management costs to less than 5%.



More than 93% of the CDMRP FY21 Appropriation Supports Scientific Research

CDMRP ACCOMPLISHMENTS AND OUTCOMES

Between October 2021 and September 2022, CDMRP executed the FY21 appropriations, initiated the execution of the FY22 appropriations, and actively managed a portfolio of innovative and impactful research projects relevant to stakeholder needs. The table below highlights notable numbers from this year's efforts:

FY21 APPROPRIATION

$1.50B	36	1,190	$1.36B
in appropriations	programs	research awards	funded research

FY22 APPROPRIATION

$1.54B	35
in appropriations	programs

BETWEEN OCTOBER 2021-SEPTEMBER 2022

6,849
managed research awards

FY22 CDMRP-FUNDED RESEARCH OUTCOMES

747	1.13K	45
publications	presentations	patents

CDMRP-FUNDED PRODUCTS

Consistent with the CDMRP's mission to fund research that discovers, develops and delivers health care solutions, research funded by the CDMRP has led to the 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 in clinical practice in 2021 or 2022.

Updates to the **National Comprehensive Cancer Care Network guidelines** show that it can be safe for some African American men to have their prostate cancer monitored through Active Surveillance, allowing them to delay aggressive and potentially unnecessary treatment and side effects. These clinical management updates were based on results from a Prostate Cancer Research Program-funded project.

The **SPRINT® Peripheral Nerve Stimulation** (PNS) System is designed to improve functional outcomes by alleviating chronic residual limb pain in patients with amputations. The Peer Reviewed Orthopaedic Research Program (PRORP), PRMRP, and Joint Warfighter Medical Research Program (JWMRP) have all contributed funds towards the development and testing of this device. In October of 2021, the SPRINT System **obtained clearance for broader clinical indication from the FDA** for use not only on the back and extremities, but also on the head, neck, and front torso.

Simoa® is a groundbreaking blood test that predicts the risk of disease activity in people with Relapsing-Remitting Multiple Sclerosis. In April 2022, the **FDA granted a Breakthrough Device designation** to Quanterix, the company that produced this test, to enable Simoa's accelerated development, assessment, and review so that patients have access to this potentially life-saving technology quicker. This novel test incorporates results from research supported by the Multiple Sclerosis Research Program.

Prosetin is a potent and selective inhibitor of motor neuron death in Amyotrophic Lateral Sclerosis (ALS). The Amyotrophic Lateral Sclerosis Research Program supported preclinical safety and efficacy studies of prosetin, which contributed to FDA orphan drug designation in 2020. **In early 2022, a phase 1 clinical trial of prosetin was initiated** to determine the optimal dose and to acquire biomarker data for future trials.

The **PleuraPath™ Chest Tube System** is a new medical technology device designed to stop thoracic blood loss and lessen the consequences of severe thoracic hemorrhage. The JWMRP supported advanced development of this technology. This project resulted in three production-ready attachments for the PleuraPath along with **submission to the FDA of a 510(k)-addendum** to include all of the attachments made under this effort.

Retired U.S. Army Sgt. 1st Class Daniel Metzdorf, PRORP Programmatic Panel Member FY22

"I have been a Consumer Reviewer for about 10 years now. Since I sat for my first CDMRP panel, my definition of Consumer Reviewer has always been 'The End User.' I am 'The End User.' The science, research, experiments, and devices that have come out of the grants through CDMRP are same as the awesome medical care that saved my life. I am the beneficiary to the countless hours of research. I wear the super human, hard core prosthetic devices that are discovered and brought to market. I get to be the voice of 'The End User,' I get the honor to champion the way forward in medical care for our Armed Forces and our Veterans. I get to be a part of the quality of life-changing care that comes from CDMRP. As 'The End User,' I am thankful for CDMRP."

COVID-19 IMPACTS

In the first half of FY22, the CDMRP continued to conduct most business meetings virtually. Beginning in the fall of 2022, the CDMRP began holding more business meetings in person and implemented a return-to-office procedure for staff, while continuing to prioritize participant safety and accessibility in light of the ongoing COVID-19 pandemic.

Additionally, CDMRP's PRMRP managed a $78.3M investment for COVID-19 related research. These funds support 24 awards related to preventing ($10.3M), detecting ($10.7M), and treating ($57.3M) COVID-19. Of these awards, 6 include expansion of ongoing PRMRP projects to include COVID research. Outcomes from these awards include:

- A $1.2M investment to Sanford Burnham Prebys Medical Discovery Institute that allowed researchers to proceed to phase 2 clinical trials and resulted in several high-profile publications, including a *Nature* paper describing that the anti-leprosy drug, clofazimine, prevents the intense inflammatory response observed in COVID-19 patients
- Humanetics Corporation used $1.3M of funding to evaluate the clinical utility of a new drug, Bio300 Oral Powder, for the prevention of pulmonary fibrosis in COVID-19-ARDS survivors and for the prevention of lung scarring
- Investigators from Colorado University developed a treatment system to inactivate whole blood pathogens, research that may lead to new SARS-CoV-2 prevention platforms

MILITARY HEALTH SYSTEM DATA INITIATIVE

CDMRP programs support high-impact research aimed at Warfighter health and readiness. While some programs target military medical issues related to active-duty service, such as injuries or conditions resulting from training, deployment, and combat, 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 beneficiaries and families, all of which ultimately impact the Military Health System (MHS). The CDMRP collaborated with the DHA Armed Forces Health Surveillance Branch to obtain MHS burden data for many of the diseases and conditions CDMRP programs are working to address. Between 2009 and 2020, millions of active-duty Service Members, former Service Members, and other DOD beneficiaries were involved in over 151 million medical encounters in the MHS for diseases and conditions CDMRP-funded research is working to address.

This data demonstrate not only the military relevance of CDMRP programs, but also help programs identify important issues related to the health and readiness of active-duty Service Members and their families as they strategically plan their program's initiatives.[1]

Between 2009 and 2020 there were

over 151 Million

medical encounters in the MHS for diseases and conditions CDMRP is working to address.

[1] As determined by data provided by the DHA Armed Forces Health Surveillance Branch to date.

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 align with public interests. Notable collaboration opportunities this year include:

- **Stakeholder meetings** for CDMRP's Military Burn Research Program and TERP
- **Reimagining Women in the Bioengineering, Technology, and Data Science Ecosystem Partnership Summit** hosted by the NIH Working Group on Women in Biomedical Careers
- **Sex, Gender, and Intersectionality Innovations Working Group** coordinated by the NIH Office of Research on Women's Health
- **Improving Ex-Vivo Models to Accelerate Therapies to Treat Hearing Loss** is a joint workshop between CDMRP's Hearing Restoration Research Program and the National Institute on Deafness and Other Communication Disorders
- **The Interagency Pain Management Collaboratory** is a jointly funded NIH, DOD, and VA effort to support large-scale pragmatic clinical trials for pain management of Veterans and Service Members
- **Federal Interagency Workgroup on Autism,** which meets to coordinate research, services, and support activities related to autism spectrum disorder
- **Interagency Collaborative to Advance Research in Epilepsy (iCARE),** which maintains a database that informs various stakeholder groups about the current funding landscape for the epilepsies

Finally, investigators and programmatic staff from federal and non-federal funding agencies serve as reviewers on CDMRP peer and programmatic review panels. Over 60 individuals representing other federal organizations served on the FY22 Programmatic Panels during 2022. These panel members bring both their expert knowledge in the field and their organization's funding strategy to better inform the future of CDMRP investments.

CDMRP MANAGING, MONITORING, AND SECURING RESEARCH ADVANCEMENTS

The newly formed Congressionally Directed Medical Research Programs' Research Integrity and Security Group (RISG) focuses on implementation of policies to manage, monitor, and secure scientific and technological advancements funded by the CDMRP. Fiscal Year 2019 and 2021 National Defense Authorization Acts require DOD-funded research be free of adversarial influences to protect our scientific and technological standing in the world. The National Security Presidential Memorandum-33 and the National Science Technology Council Guidance provides guidance to all Federal agencies and departments regarding five key Areas of Interests including: funded applicants' disclosure of foreign collaborations, requirement for the use of digital persistent identifiers, consequences for the violations of disclosure requirements, Federal-wide information sharing, and the formation of research security programs. In response, the RISG ensures the CDMRP applies all current laws and policies regarding science and technology protections according to DOD regulations.


ARMY
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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 USE DISORDERS RESEARCH PROGRAM

Exploring integrated approaches to identify pharmacotherapeutics for ASUD, especially comorbid ASUD with PTSD and other psychological disorders

Aim 1 – Discover: Test new chemical entities and repurpose existing medications in preclinical and non-clinical models.

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.

Aim 3 – Phase 2 Efficacy: Conduct multiple-site clinical trials to test the preliminary efficacy and safety of potential medications or medication combinations in humans, and to explore precision medicine tools for matching patients to these medications.

Scan me to access even more information about the 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 AND GOALS

Alcohol and substance use disorders (ASUD) are a growing concern among the general public, military personnel, and Veterans – even more so if accompanied by Post Traumatic Stress Disorder (PTSD). Service Members with family struggling with addiction often find it difficult to focus on their military mission. Furthermore, people who develop an opioid dependency following an injury generally struggle with addiction.

The report "Substance Use Disorders in the U.S. Armed Forces"[1] highlighted the growing medical burden imposed on the Military Health System (MHS) by excessive alcohol use. Congress 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. In response, the DOD assumed leadership to ensure that consistent and quality treatment services were available to those with ASUD.

The Peer Reviewed Alcohol and Substance Use Disorders Research Program (ASUDRP) has established a network of multidisciplinary, translational research teams with the explicit goal of accelerating the delivery of new or improved treatments for ASUD. The ASUDRP has distributed a total of $52.1M to relevant research. The ASUDRP did not receive an appropriation in FY20, but continued to manage open awards. In FY21 Congress appropriated $4M to the ASUDRP, recognizing the ongoing threat posed by the opioid epidemic.

The program's goal is to explore integrated approaches to address ASUD, especially comorbid ASUD with PTSD and other psychological disorders, and to reduce the number of opioid and other substance use-related deaths through multidisciplinary, team-based research that translates basic knowledge into enhanced clinical pharmacological treatment protocols and improved quality of life for Service Members, Veterans, and the public.

[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/

2021 Congressional Appropriations, Research Investment, and Withholds and Management Costs

Congressional Appropriations	*Research Investment*	*Withholds and Management Costs*
$4M	Consortium Award ..... $3,525,000 Modification to ongoing awards $87,660	USAMRDC ..... $77,340 SBIR/STTR ..... $133,000 Mgt Costs (4.67%) $177,000
Total: $4M	**Total:** $3,612,660	**Total:** $387,340

Identifying Compounds to Treat Opiate Use Disorder by Leveraging Multi-Omic Data Integration and Multiple Drug Repurposing Databases

Dr. Bradley T. Webb, RTI International

Military Service Members and Veterans are at increased risk for opiate use disorder (OUD). Recent discoveries in genome-wide association studies (GWAS), protein-protein interactions, and gene expression research domains are increasing the understanding of the biology of OUD. However, a gap exists between translating this biological insight into effective therapies. To address this gap, we are constructing a framework to integrate cross-domain research evidence to identify and prioritize new biological targets for repurposing approved or clinically advanced medications for treatment of OUD. This study leverages two large-scale GWAS studies, four post-mortem human brain gene expression results, and network analyses of protein-protein interactions in human brain to identify 24 gene targets. Querying four drug repurposing databases identified approved compounds that target six of these OUD-associated gene targets for follow-up review by drug-repurposing experts. Querying multiple lines of evidence:

- allows simultaneous querying of many genes of interest,
- detects candidates missed using a single domain, and
- produces succinct summaries to facilitate efficient expert review.

By identifying larger pools of candidate medications and summarizing the supporting biological evidence, we are able to bridge the gap between discovery and translational studies.

MEASURING SUCCESS

Conduct studies of new medications to treat ASUDs

- 32 funded institutions/ 46 projects
- 52 published papers
- 1 patent application
- 7 Food and Drug Administration (FDA)-approved currently active Investigational New Drug applications
- 35 projects focused on AUD or SUD

Special emphasis on comorbidities of traumatic brain injury (TBI) and post-traumatic stress disorder (PTSD) in populations of Service Members and Veterans

- 2 clinical trials on active-duty populations (Fort Gordon and Point Loma)
- 15 clinical trials at VA Medical Centers

Use a translational approach to understand the complex interaction of ASUDs with the military stress comorbidities of PTSD and TBI

- 8 active pharmaceutical collaborators
- 2 compounds transitioned to the pharmaceutical industry for further development
- 23 preclinical and 22 clinical projects
- 1 compound being studied by both Pharmacotherapies for Alcohol and Substance Use Disorder Alliance and National Institute on Alcohol Abuse and Alcoholism

Retired U.S. Army SPC Robert Elder, Veterans Engagement Board, Programmatic Panel Member FY21-FY22

"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."

AREAS OF EMPHASIS

- Improved formulations to treat ASUD with comorbid substance use
- Improved formulations to treat ASUD with comorbid PTSD and other psychological disorders
- Stronger, longer-duration formulations to counteract opioid (including fentanyl analogs) overdose
- New formulations and/or combinations of existing medications to improve treatment compliance, prevent relapse, and reduce risk of misuse
- Novel medications and immunotherapies to treat substance and/or ASUD
- New medication targets for the treatment of substance and/or ASUD

AMYOTROPHIC LATERAL SCLEROSIS RESEARCH PROGRAM

VISION

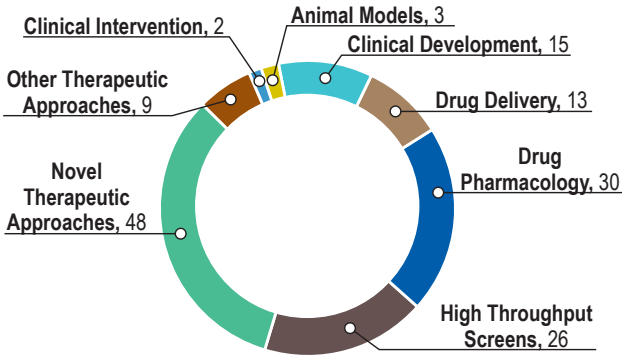
Improve treatments and find cures for people with ALS

MISSION

Fund impactful research to develop ALS treatments

PROGRAM HISTORY

The Amyotrophic Lateral Sclerosis Research Program (ALSRP) was initiated in FY07 when the DOD redirected $5M of Army Research, Development, Test, and Evaluation funding for the CDMRP to initiate the ALSRP as a broadly competed, peer-reviewed research program. Appropriations have totaled $149.4M, including $40M in FY21. The portfolio focuses on therapeutic discovery and preclinical validation aimed at identifying new amyotrophic lateral sclerosis (ALS) drug candidates and moving them into advanced drug development. Recent increases in the ALSRP appropriation, from $20M in FY20 to $40M in FY21, have enabled the program to increase investments in innovative therapeutic approaches and to support clincial trials.



ALSRP Portfolio by Number of Projects FY07-FY21

FOCUS

Since inception and over a 15-year history of congressional support, the ALSRP has changed the landscape of research and energized the ALS research community to conduct high-risk research that is innovative and impactful, ultimately aiming to cure the disease. The ALSRP made unprecedented inroads in supporting the development of new treatments and is the leading supporter of hypothesis-driven drug discovery. The program investments in drug discovery, Investigational New Drug-enabling studies, critical biomarker studies, and early phase interventions continue to promote responsible translational science.

RELEVANCE TO THE MILITARY

- Scientific evidence demonstrates that those who serve in the military — regardless of branch, location, or peace time or time of war — are at a greater risk of dying from ALS than if they had never served.
- Reasons for increased risk have been linked to chemical exposure, traumatic brain injury, viral infection, and intense physical activity. However, no definitive link has been established.

Scan me to access even more information about the program.

Nadia Sethi, I AM ALS, Programmatic Panel Member FY21-FY22

"I am so grateful for the opportunity to share information where it can make a tangible impact on ALS research. When facing ALS, we live on hope. These grants, this science, and the clinical trials born from them are our hope."

2021 Congressional Appropriations, Research Investment, and Withholds and Management Costs

Congressional Appropriations	*Research Investment*		*Withholds and Management Costs*	
$40M	Clinical Development Award	$6,338,098	USAMRDC	$774,397
	Therapeutic Development Award	$6,900,128	SBIR/STTR	$1,334,000
	Therapeutic/Biomarker Pilot Trial Award	$6,646,704	Mgt Costs (3.22%)	$1,220,108
	Therapeutic Idea Award	$16,253,542		
	Modification to ongoing awards	$533,023		
Total: $40M		**Total:** $36,671,495		**Total:** $3,328,505

Maintaining the bridge from discoveries in the laboratory to advanced therapeutic development and clinical trials

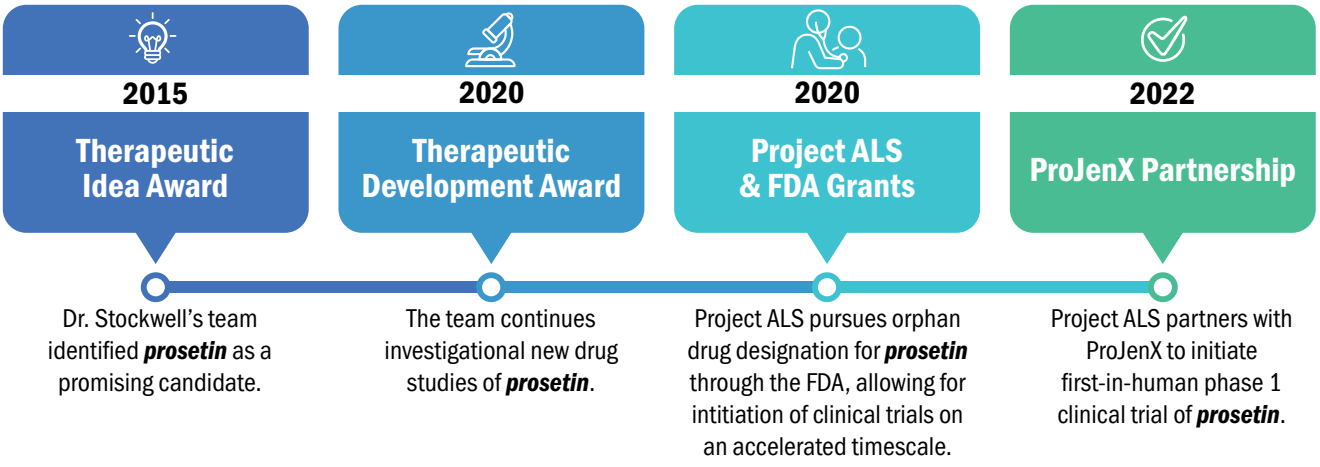
A New Compound to Prevent Motor Neuron Toxicity in ALS Enters Clinical Trial

Dr. Brent Stockwell and Dr. Hynek Wichterle, Columbia University

Dr. Brent Stockwell and his team used an FY15 Therapeutic Idea Award to develop selective inhibitors of endoplasmic reticulum stress ALS models and identified prosetin, a brain-penetrant kinase inhibitor, as a promising candidate. The team further obtained an FY20 Therapeutic Development Award (TDA) to evaluate pharmacology, safety, and efficacy profiles of prosetin across multiple models of ALS. Under the TDA, the team identified a clinical formulation for prosetin delivery, evaluated the toxicokinetic profile of prosetin, and generated sufficient GMP-grade material to proceed with clinical trials. Validation of a biomarker for kinase target engagement, with the possibility of expanding to include samples from the clinical trial, is ongoing.

Dr. Brent Stockwell, Columbia University, ALSRP-Funded Investigator

"Our ultimate aim is to deliver a meaningful therapy to people with ALS, and because our primary responsibility is to the ALS community, we will conduct this research of prosetin with the urgency and rigor that this disease demands."



ALSRP works synergistically with other funders to advance ALS research along the development pipeline

CDC
Objective: Estimate cases, understand who, examine connections, improve care

NIH
Objective: Seek fundamental knowledge about the brain and nervous system and use that knowledge to reduce the burden of neurological disease

DOD ALSRP
Objective: Expedite the pathway from bench science to clinical trials for new therapeutic approaches aimed at controlling or curing ALS

Industry
Objective: Advance treatments to patients through clinical trials, precision medicine, and assistive technology

- **The Centers for Disease Control and Prevention (CDC)** is currently the largest funder of ALS epidemiology, estimating cases, understanding who, and examining connections, including within the military population.
- **The National Institutes of Health (NIH)** is currently the largest funder of mechanistic ALS research and model development, primarily investigating basic biology and genetics.
- **ALSRP** is the largest funder of innovative drug discovery, leveraging what is learned from other funders to ultimately inform and de-risk clinical trials of new therapeutic approaches.
- **Industry** is the largest funder of large-scale clinical trials of ALS therapeutics. Promising development moves from the ALSRP into the private sector for advanced development and later stage confirmation trials.

AUTISM RESEARCH PROGRAM

Autism Spectrum Disorders affect 1:44 children in the U.S., where males are four times more likely to be diagnosed than females. Within the MHS, there were more than 60,000 new ASD cases for military beneficiaries reported from 2009-2018.

Scan me to access even more information about the program.

VISION *Improve the lives of individuals with autism spectrum disorders now*

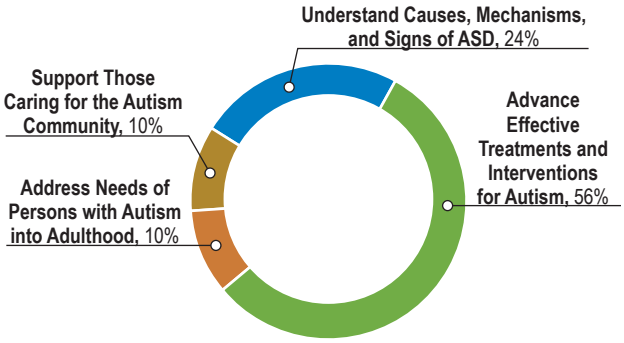
MISSION *Promote innovative research that advances the understanding of autism spectrum disorder and leads to improved outcomes for Service Members, their families, and the American public*

PROGRAM HISTORY

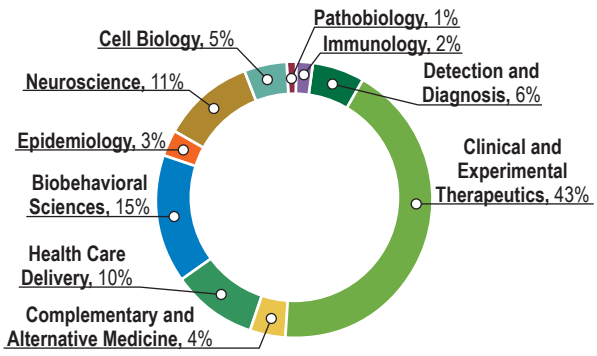
Since its inception in FY07, through FY21, appropriations totaling $134.4M have been directed to the Autism Research Program (ARP) to promote innovative research that advances the understanding of autism spectrum disorder (ASD). The immediacy of ARP's vision, to improve the lives of individuals with ASD now, has imparted a strong sense of action and continues to steer the ARP's investment strategy. ARP focuses on funding innovative and highly impactful research while trying to complement other funding agencies' initiatives.

INVESTMENT STRATEGY

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 health care 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 gastrointestinal issues, sleep, and anxiety; (3) understanding the needs of adult individuals with ASD; and (4) supporting those caring for the autism community.



ARP Portfolio by Strategic Goal FY17-FY21



ARP Portfolio by Research Type FY16-FY21

2021 Congressional Appropriations, Research Investment, and Withholds and Management Costs

Congressional Appropriations	*Research Investment*	*Withholds and Management Costs*
$15M	Career Development Award.....$3,697,682 Clinical Translational Award .....$924,442 Clinical Trial Award.....$4,916,788 Idea Development Award $3,766,038	USAMRDC .....$287,054 SBIR/STTR ..... $501,000 Mgt Costs (4.57%) $907,157
Total: $15M	**Total:** $13,304,950	**Total:** $1,695,211

ARP-FUNDED EARLY CAREER INVESTIGATORS

The ARP is committed to supporting early-career investigators in the field of autism, as one of the key elements in the program's strategic direction is to support the development of an early-stage diverse investigator cohort for autism research. The following five early-career investigators are examining ideas that will further both the field of autism research and their careers.

Juan Dipini, Autism Speaks, Consumer Peer Reviewer FY21-FY22

"It is disheartening to see how many families struggle daily when they lack resources, [and experience a] scarcity of medical services, support, or information. As a parent, I find the ARP valuable because it not only involves parents and their input, but [also] the fusion of the scientific community and ASD families."

Dismantling the "Visual Ease Assumption": Cross-Modal Examinations of Narrative Comprehension in Individuals with Autism

Dr. Emily Coderre, University of Vermont & State Agricultural College

Dr. Coderre is a cognitive neuroscientist who is investigating language and narrative comprehension as it relates to autism. In her ARP-funded study, participants aged 18-35 will navigate a series of visual and linguistic tasks designed to isolate the subfunctions of interest. Dr. Coderre and her team aim to better characterize the strengths and challenges that autism brings in narrative comprehension. The team will determine which narrative subfunctions pose difficulties for autistic individuals and whether these subfunctions work differently between visual and verbal narratives, as well as how they contribute to narrative comprehension overall.

Is There a Point of Convergence Between Congenital Heart Disease and Autism?

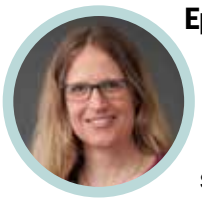
Dr. Jason Tchieu, Cincinnati Children's Hospital

Throughout his career, Dr. Tchieu has investigated stem cell engineering, developmental neurobiology, and genome editing and has studied many biochemical processes to establish an understanding of how disease manifests. In his Career Development Award study, Dr. Tchieu and his team will investigate shared mechanisms involved with congenital heart defects (CHD) and ASD. He hypothesizes that a subset of mutations within the WNT pathway, a cellular process important for cellular differentiation and development, increases the risk of both ASD and CHD. This study aims to develop future predictive or diagnostic tools focused on therapeutically targeting CHD in the ASD population.

Atypical Thalamocortical Connectivity and Its Relationship to Sleep Problems and Sound Processing in Young Children with Autism Spectrum Disorders

Dr. Annika Linke, San Diego State University

Dr. Linke is well versed in using advanced neuroimaging techniques to study sensory processing, and she is interested in the relationship between sleep quality, sensory processing, and behavior in ASD. Using these techniques, her team will study the role of increased connections between the thalamus and sensory cortices of the brain, combined with imbalances in neural excitation and inhibition, and the relationship of sleep disturbances with atypical auditory processing in ASD. This project will be a first step in identifying neural mechanisms underlying sleep.



Epigenetics in Autism: An In Vivo PET Imaging Study

Dr. Nicole Zürcher Wimmer, Massachusetts General Hospital

Dr. Zürcher Wimmer is interested in using neuroimaging techniques to study the biology underlying ASD. Alterations in histone deacetylases (HDACs) levels may be linked with environmental risk factors for ASD, such as parental age, toxins/pollution, early-life immune insults, and maternal stress and obesity. This project will test the hypothesis that HDACs are altered in individuals with ASD compared with age-, sex-, and IQ-matched individuals without ASD. She will also investigate if there are sex-specific differences in HDACs that might help explain the increased incidence of ASD in males.

Brainwide Social Network in Mice Underlying Autism Spectrum Disorder

Dr. Ariel Gilad, Hebrew University of Jerusalem

Dr. Gilad is interested in linking brain activity to genetic and molecular mechanisms. He hypothesizes that social networks are brain-wide and dynamic, and that ASD symptoms can be linked to an underlying network deficit. To study this, he and his team have developed a method of recording several brain areas at once, and they will be analyzing the social network motifs of several ASD model mice and comparing the networks to normal wild-type mice. Dr. Gilad hopes the insights gained from this project will improve understanding of the heterogeneity of ASD by mapping the social brain from an individual perspective.

BONE MARROW FAILURE RESEARCH PROGRAM

Scan me to access even more information about the program.

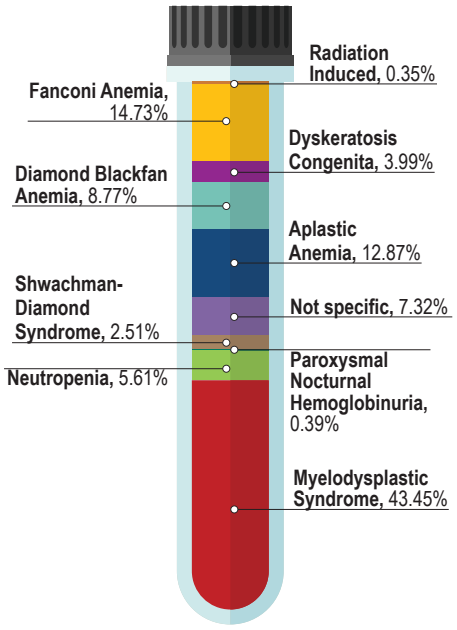
VISION *To understand and cure bone marrow failure diseases*

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

The Peer Reviewed Bone Marrow Failure Research Program (BMFRP) was initiated in FY08 to provide support for exceptional innovative research focused on Bone Marrow Failure (BMF) diseases. From FY08 through FY21, Congress has appropriated $49.05M to research the prevention, causes, and treatment of BMF diseases. Thus far, the BMFRP has funded 92 awards, with the mission to support innovative research committed to advancing the understanding of inherited and acquired BMF diseases. A recent increase in funding has provided the program the opportunity to fund more projects with increased scope, maturity, and translatability, hopefully increasing our impact on research and patient care. The appropriation for FY22 for the BMFRP is $7.5M.

BMF diseases can be either inherited or acquired and, regardless of etiology, may lead to lifelong chronic illnesses with increased risk for cancer development. Inherited BMF includes a group of diseases in which genetic mutations lead to a deficiency in hematopoiesis that presents itself in childhood or early adulthood. Examples are Fanconi anemia, Dyskeratosis congenita, Shwachman-Diamond syndrome, Diamond-Blackfan anemia, and severe congenital neutropenia. 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. Examples are Aplastic anemia, myelodysplastic syndrome (MDS), maroxysmal nocturnal hemoglobinuria, and pure red cell aplasia.



Investment by BMF Disease Type FY08-FY21

2021 Congressional Appropriations, Research Investment, and Withholds and Management Costs

Congressional Appropriations	*Research Investment*	*Withholds and Management Costs*
$7.5M	Idea Development Award – Early Career Investigator.....$2,071,289 Idea Development Award – Established Investigator..... $3,924,463 Investigator-Initiated Research Award–Funding Level 1..... $911,777	USAMRDC ..... $144,889 SBIR/STTR ..... $250,000 Mgt Costs (2.78%) $197,582
Total: $7.5M	**Total:** $6,907,529	**Total:** $592,471

Matthew Pearl, Fanconi Anemia Research Fund, Consumer Peer Reviewer FY21-FY22

"It was an honor to work with the Bone Marrow Failure Research Program, using my experiences and expertise to put purpose to pain, helping others. My sister, Alexandra, and I both have a rare genetic blood disorder called Fanconi anemia (FA). FA makes life extremely complicated, challenging, and confusing, but I would not change who I am. FA has been my greatest teacher, keeping me in check of how fragile life is, while death takes undeserving friends too soon. I am grateful to be able to bring my input to the BMFRP, change lives, and bring awareness to all going through bone marrow failure."

FY21 Summary of Funded Research

Focus Area: Understand Causes and Progression

Myelodysplastic Syndrome

Human and Mouse Models of DDX41-Mutated Myelodysplastic Syndrome
Children's Hospital, Cincinnati, Dr. Timothy Chlon
To determine how recurring co-mutations, such as p53 loss, coordinate with inherited and acquired DDX41 mutations to cause MDS. Also, to identify therapeutically targetable pathways in DDX41-mutant MDS.

Mitochondrial Dynamics as a Therapy Target in MDS
New York University School of Medicine, Dr. Ioannis Aifantis
To identify mechanisms of resistance from Venetoclax treatment in MDS patients and propose therapeutic options to circumvent drug resistance by introducing a novel compound that strongly synergizes with apoptosis-inducing agents.

The Role of U2AF1 Mutations in Myelodysplastic Syndrome: A Noncanonical Role for Splicing Factors in Bone Marrow Failure
National Cancer Institute, Dr. Daniel Larson
To examine the process of gene regulation at the level of RNA translation into protein, and characterize the role of U2AF in regulating the cytokine family of genes, which are important mediators of inflammation in the bone marrow.

Cooperative Events in the Evolution of Monosomy 7 Myelodysplastic Syndrome
University of Rochester, Dr. Archibald Perkins
To use several innovative mouse strains for determining the genetic process by which MDS patients progress to AML.

Fanconi Anemia

Defects in the Transition from Neonatal to Adult HSCs as the Etiology and a Therapeutic Target in Fanconi Anemia
Children's Hospital, Cincinnati, Dr. Paul Andreassen
A defect in the transition from neonatal to adult hematopoietic stem cells (HSCs), resulting from dysregulation of R-loops and/or stress granulopoiesis, is explored as a mechanism that drives BMF in FA and which could provide a basis for novel therapies.

Additional project information, including award abstracts, can be found on the CDMRP award search page https://cdmrp.health.mil/search.aspx

Focus Area: Find Effective Treatments and Cures

Aplastic Anemia

Developing FAS-Resistant, Bone Marrow-Tropic Regulatory T Cells (Tregs) for the Treatment of Immune Aplastic Anemia
King's College, London, Dr. Shahram Kordasti
To overcome the low Tregs manifested in AA by making them resistant to early cell death in the inflammatory environment and enhancing their recirculation to the bone marrow. Also seeks to test the function and longevity of these Tregs in a hostile and inflammatory environment.

Myelodysplastic Syndrome

Activating Anti-MDS Immunity Through Restoration of the Immune Microenvironment
Health Research, Inc., Roswell Park Division, Dr. Michael Nemeth
To study how dendritic cell vaccines can improve survival outcomes in patients with MDS.

Targeting Muscarinic Acetylcholine Receptor Pathway in Myelodysplastic Syndrome
Cold Spring Harbor Laboratory, Dr. Lingbo Zhang
To overcome treatment resistances by targeting a protein CHRM4 (which promotes the bone marrow's ability to produce red blood cells) in the treatment of anemia in MDS.

Neutropenia

Development of Base Editing for Gene Therapy of ELANE-Mutated Severe Congenital Neutropenia
University of Massachusetts Medical School, Dr. Peter Newburger
To treat congenital neutropenia using a gene-editing method which would allow the affected bone marrow to produce the neutrophils needed for protection from bacterial infections.

Fanconi Anemia

In Vivo Delivery of Precise Gene Correction for Treatment of Fanconi Anemia
St. Vincent's Institute of Medical Research, Dr. Andrew Deans
To reverse DNA changes that lead to FA by using two cutting-edge technologies, programmable mammalian baculovirus (BacMam) and a Cas9-based prime editing, in order to correct the causative mutations and restore normal blood production.

BREAST CANCER RESEARCH PROGRAM

VISION *A world without breast cancer*

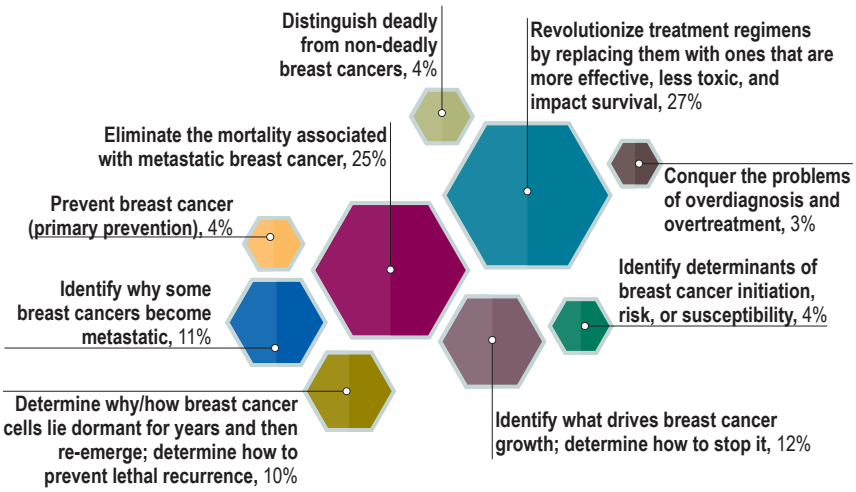
MISSION *To end breast cancer for Service Members, Veterans, and the general public by funding innovative, high-impact research through a partnership of scientists and consumers*

PROGRAM HISTORY

The DOD Peer Reviewed Breast Cancer Research Program (BCRP) was established in 1992 as a result of the dedicated efforts of breast cancer advocates. Their continued efforts, in concert with the program's accomplishments, have resulted in more than $4 billion (B) in congressional appropriations through FY22. Research supported by the BCRP has led to the development of new standard-of-care treatments, diagnostic and imaging approaches, risk-assessment tests, and resources for research and patient communities.

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:[2]



BCRP Portfolio Investment by Overarching Challenge FY13-FY21

IMPACT IN THE MILITARY HEALTH SYSTEM

Preclinical research supported by the BCRP contributed to four FDA-approved drugs: trastuzumab, palbociclib, ribociclib, and abemaciclib. For these drugs, between 2007 through 2018 there were:

- Over **34,600** prescriptions written for more than **2,400** MHS patients including active-duty Service Members and DOD beneficiaries with TRICARE coverage.[1]

Scan me to access even more information about the program.

[1] Source: Defense Health Agency Pharmacy Analytics Support Section
[2] https://cdmrp.health.mil/bcrp/pdfs/BreastCancerLandscape2022.pdf

2021 Congressional Appropriations, Research Investment, and Withholds and Management Costs

Congressional Appropriations	*Research Investment*		*Withholds and Management Costs*	
$150M for Breast Cancer Research	Breakthrough Award – Funding Levels 1 and 2	$71,772,231	USAMRDC	$2,899,940
$476,683 proceeds from the Stamp Out Breast Cancer Act	Breakthrough Award Level 3	$7,379,025	SBIR/STTR	$5,003,000
	Era of Hope Scholar Award	$4,798,164	Mgt Costs (5.36%)	$7,610,419
	Expansion Award	$4,338,507		
	Transformative Breast Cancer Consortium Award	$38,261,346		
	Modification to ongoing awards	$8,414,051		
Total: $150,476,683		**Total:** $134,963,324		**Total:** $15,513,359

RESEARCH ADVANCES FOR ASSESSING PROGNOSIS

A Gene Panel to Predict Risk of Recurrence in Patients

Dr. Christopher Li, Fred Hutchinson Cancer Research Center
Dr. Arul Chinnaiyan, University of Michigan

The research team developed and completed initial validation testing of a gene panel (BRAVO-DX) shown to be a strong predictor of recurrence-free survival in patients with basal-like breast cancer (BLBC). In addition to developing the BRAVO-DX panel, the researchers identified cellular characteristics with potential for future use as biomarkers to inform treatment of BLBC.

Stromal Lysyl Hydroxylase 2, a Novel Biomarker for Patient Prognosis

Dr. Ori Maller and Dr. Valerie Weaver, University of California, San Francisco

The research team identified stromal lysyl hydroxylase 2 (LH2) as a novel biomarker and potentially early prognostic indicator of metastatic breast cancer disease aggression and poor patient survival. The findings support future investigation to confirm whether a causal relationship exists between stromal LH2, tumor aggression, and metastasis.

CLINICAL TRIALS FOCUSED ON METASTATIC BREAST CANCER

Novel Immunotherapy for Brain-Metastatic Breast Cancer (BMBC)

Dr. Pawel Kalinski, Roswell Park Comprehensive Cancer Center
Dr. Brian Czerniecki, Moffitt Cancer Center

The investigators are conducting clinical testing of a novel immunotherapy for patients with BMBC and determining the underlying mechanisms of therapeutic effects. A phase 2 trial of the vaccines combined with pembrolizumab for treatment of patients with parenchymal BMBC opened for accrual in 2022. A phase 1 trial for the treatment of patients with leptomeningeal disease is also planned. [NCT04348747]

Targeting the Stromal Compartment to Limit Breast Cancer Progression and Abrogate Therapy-Induced Morbidities

Dr. Sheila Stewart and Dr. Cynthia Ma, Washington University

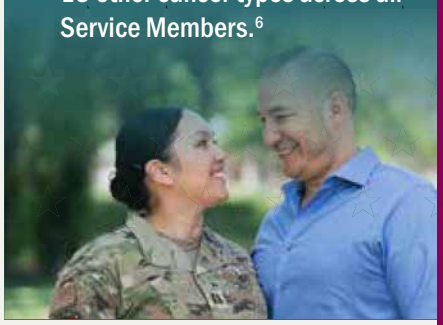
The investigators are studying the mechanisms whereby MK2 inhibitors limit metastatic tumor progression and bone loss, and they will conduct a phase 1/2 clinical trial of an MK2 inhibitor combined with chemotherapy for the treatment of patients with metastatic breast cancer. The trial will evaluate the safety and effectiveness of this treatment to limit disease progression, along with disease- and chemotherapy-induced bone loss.

TeMaya Eatmon, Living Beyond Breast Cancer, Consumer Peer Reviewer FY17-FY20

"I consider it a privilege to be a part of ensuring that the DOD BCRP grants are impactful with the hope to eradicate breast cancer or at least to change the trajectory for those with breast cancer, including young women of color like myself. The DOD BCRP program is the machine behind the innovation and the medications and therapies that are being studied and developed to ensure that future breast cancer patients will not have to deal with the unbearable side effects that we are experiencing today."

RELEVANCE TO MILITARY HEALTH

- Breast cancer is the most common non-skin cancer in women, causing the most cancer-related deaths in women under the age of 40. [3,4]
- Female active-duty Service Members have a 20%-40% higher incidence rate of breast cancer than the general public.[5]
- 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.[6]



[3] https://gis.cdc.gov/Cancer/USCS/#/AtAGlance/
[4] https://seer.cancer.gov/statfacts/html/aya.html
[5] PMID: 19505907
[6] PMID: 27501939

CHRONIC PAIN MANAGEMENT RESEARCH PROGRAM

Scan me to access even more information about the program.

VISION

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

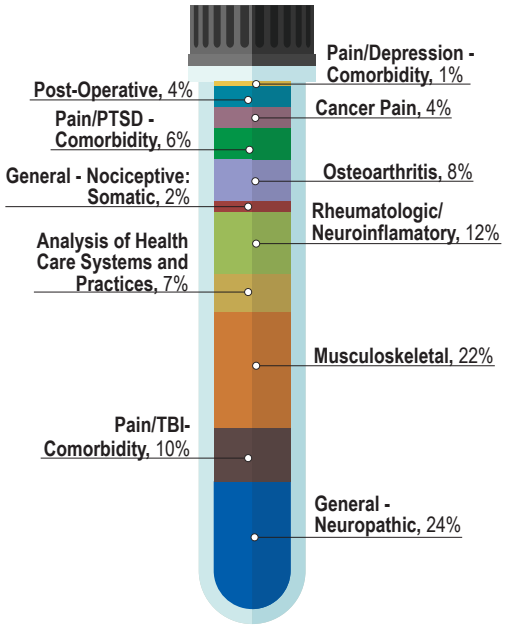
MISSION

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 more than $174M in chronic pain research. The CDMRP also participates in the Pain Management Collaboratory, an interagency effort with the NIH and U.S. Department of Veterans Affairs (VA) supporting pragmatic clinical trials for non-pharmacological approaches to pain management.

Through FY21, the CPMRP managed $40M in congressional appropriations. Of the FY19-FY21 funds, 20% supported research either conducted at a DOD or VA facility or included collaborations with affiliated staff. Through FY21, the CPMRP received a total of 223 compliant applications: 34 for Translational Research Awards (TRA) and 166 for Investigator-Initiated Research Awards (IIRA). New in FY21, the program offered the Clinical Exploration Award (CEA) to support highly innovative avenues of chronic pain management, and it received 23 compliant applications. Following the recommendations from the CPMRP Programmatic Panel members, the CPMRP has funded 5 TRAs, 20 IIRAs, and 1 CEA.



CPMRP Portfolio Investment by Pain Type FY19-FY21

2021 Congressional Appropriations, Research Investment, and Withholds and Management Costs

Congressional Appropriations	*Research Investment*	*Withholds and Management Costs*
$15M	Clinical Exploration Award – Clinical Trial ..... $325,137 Investigator-Initiated Research Award ..... $4,326,071 Investigator-Initiated Research Award – Partnering PI Option ..... $4,006,733 Translational Research Award – Single PI Only ..... $2,206,031 Translational Research Award – Partnering PI Option ..... $2,152,701 Modification to ongoing awards $393,059	USAMRDC ..... $289,965 SBIR/STTR ..... $501,000 Mgt Costs (5.63%) $799,303
Total: $15M	**Total:** $13,409,732	**Total:** $1,590,268

Since its establishment, the CPMRP has placed significant value on stakeholder engagement and has included it as an area of encouragement in all of the funding opportunities. From patients to their families, patient advocates, community leaders, medical professionals, health care administrators, decision and policy makers, and military collaborators, there are a diverse complement of views, opinions, perspectives, and priorities to consider when developing and optimizing pain management approaches. The overall impact a treatment makes on clinical care is not only grounded in efficacy but also acceptance, utilization, and preferential attitudes.

The CPMRP challenges our funded investigators to actively engage stakeholders at different ecological levels of patient care to gain situational awareness, learn from the stakeholder's experiences and preferences, and use that information to shape their research questions and approaches. Beginning in FY22, all applications submitted to our patient-centric TRA will require applicants to include two key stakeholders as members of the research team. As has been the case since FY19, all applicants are encouraged to engage members from the following segments of the chronic pain community, as appropriate to the proposed research:

Key Stakeholders: Patients, care providers, patient advocates, and community leaders. Individuals either directly touched by chronic pain or advocating on their behalf can provide key insights into the most pressing issues effecting the chronic pain community. They help to ensure pain management strategies are agreeable with patients to support adherence to treatment protocols and fidelity in long-term utilization.

Medical Professionals: Nurses, physicians, behavioral health consultants, physical therapists, and other medical staff. Medical professionals that regularly treat chronic pain patients have a distinct perspective and can speak to the effectiveness of pain management strategies within and across populations effected by different chronic pain etiologies and comorbidities. As partners in patient care, they can speak to efficiencies and challenges in delivery of different health care modalities, including training of self-management approaches.

Hospital/Health Care Administrators, Policy & Decision Makers: Optimal utilization of any pain management strategy, but particularly for non-pharmacological complementary and integrative health care approaches, requires proper resources and appropriately trained staff. Engagement of administrators and policy makers helps foster a better understanding of the current conditions and limitations within health care systems, and allows for long-term strategic planning of staffing and resource allocation to adopt promising new approaches.

Military Collaborators: Clinical studies conducted in Military Treatment Facilities have distinct stakeholders whose support is critical for project success. Onsite collaborators and co-investigators play an essential role in navigating the unique considerations of performing research in the MHS and facilitate stakeholder engagement with local commanders, senior military leaders, and potential study participants. CPMRP researchers are encouraged to read and consider these challenges as described in in a 2021 Military Medicine article.[1]

[1] Rhon DI, Oh RC, and Teyhen DS. 2021. Challenges with engaging military stakeholders for clinical research at the point of care in the U.S. Military Health System. Military Medicine; usab494. https://pubmed.ncbi.nlm.nih.gov/34962279/

MAJ Daniel Rhon, USA Retired P.T., D.P.T., D.Sc., Brooke Army Medical Center, Progammatic Panel Member FY19-FY22

"Our Service Members sustain a disproportionately high rate of injuries as a unique occupational hazard. A substantial portion continue to have persistent symptoms with chronic sequela, causing disability, loss of function, and reduced quality of life. Many advances in the field of pain management have been made, but there is much work still to be done. We owe our Service Members persistence in our resolve and commitment to continue learning how we can improve the care they receive, to minimize the consequences due to the sacrifices so many have made. It's a privilege to be a part of the CPMRP spearheading these efforts."

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 improve medical readiness, optimally diagnose and treat life-threatening injuries, reduce fatalities, and promote positive long-term outcomes for the Warfighter

PROGRAM HISTORY

The Combat Readiness – Medical Research Program (CRRP) was established in FY19 to fund 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. Additional Areas of Interest include 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. From FY19 through FY22, CRRP received $45M in congressional appropriations. 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 (Figure 1). 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.

FY22 FOCUS AREAS

- Solutions to enhance combat care delivery throughout the far-forward environment
- Wound care solutions for complex trauma and tissue regeneration that span the operational medical care continuum or roles of care
- Solutions to enhance Warfighter readiness

Scan me to access even more information about the program.

FY22 INVESTMENT STRATEGY

In FY22, the CRRP plans to fund four Rapid Development and Translational Research Awards of $2.2M each, for a total estimated research allocation of $8.7M out of a total $10M in congressional appropriations.

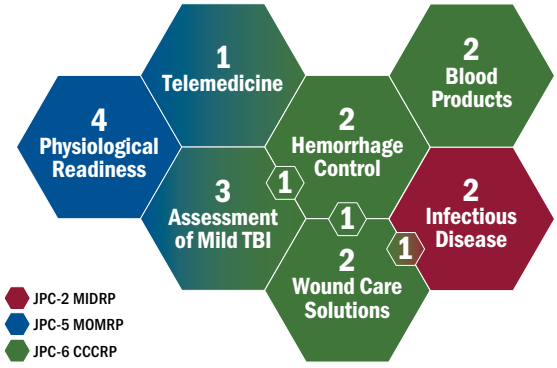


Figure 1. Synergistic alignment of funded CRRP projects to DHP Core research program areas

MIDRP - Military Infections Diseases Research Program; MOMRP - Military Operational Medicine Research Program; CCCRP - Combat Casualty Care Research Program; DHP - Defense Health Program

2021 Congressional Appropriations, Research Investment, and Withholds and Management Costs

Congressional Appropriations	*Research Investment*	*Withholds and Management Costs*
$10M	Rapid Development and Translational Research Award $9,056,189	USAMRDC ..... $193,340 SBIR/STTR ..... $333,000 Mgt Costs (4.41%)..... $417,471
Total: $10M	**Total:** $9,056,189	**Total:** $943,811

HIGHLIGHTS

Prevention of Surgical Hypothermia Using Non-Electric Fluid Warmers

Dr. Arfi Rahman, MaxQ Research, LLC

Most blood products are stored under cold conditions and must be warmed to body temperature to be administered to patients. Portable warmers are helpful in a far-forward environment but are limited by their small processing capacity, size, and reliance on electric power. Dr. Rahman is developing a new device that is smaller, easier to use, more robust, and able to be used without electricity. His new technology, the MaxExo™ fluid warmer, will use a controlled chemical reaction to warm reconstituted freeze-dried plasma in the field. In conjunction with military and civilian stakeholders, Dr. Rahman and team created a list of eight operational requirements to guide the development and field evaluation of the device. Several different chemical reactions are currently being evaluated to determine the optimal warming characteristics for the device. The team is also using the guidelines to ensure the chosen chemistry is the most efficient and user-friendly.

Wearable Neurotechnology for Treatment of Insomnia

Dr. Stephen Simons, Teledyne Scientific & Imaging, LLC

Insomnia is a significant concern for the military due the effects on combat readiness and persistence in Veteran populations. Currently, treatments for insomnia are not ideal due to medication side effects and compliance issues for behavioral therapy. Dr. Simons plans a feasibility study to test the safety and efficacy of the Teledyne PeakSleep™, a wearable device for treatment of insomnia that is worn prior to sleep. The device stimulates the brain with electrical pulses to encourage preparation for sleep. The study will be completed in an active-duty Service Member population at Walter Reed National Military Medical Center. After feasibility testing, the device will be adapted to combat settings by increasing its ruggedness. If successful, PeakSleep is a potential easy-to-use and safe treatment for insomnia, which could reduce fatigue and increase combat readiness.

Development of a Temperature-Stable Broad-Spectrum Antiviral for Respiratory Viral Pathogens

Dr. Bryan Berube, HDT Bio Corp

Accidental and intentional exposure to viruses is a significant concern in the military. Current antiviral drugs inhibit viral replication and can lead to resistance. Retinoic acid-inducible gene I (RIG-1), a protein recognizing viral nucleic acids, stimulates the immune system and is an alternative mechanism of antiviral therapy, but current delivery methods of RIG-1 therapeutics lack safety and efficacy. Bryan Berube and HDT Bio Corp have developed a RIG-1 activating RNA (RAR) as an antiviral therapy. To address the safety and efficacy concerns, the team will pair RAR with LION™, a nanoparticle proven to be safe and effective for delivery of RNA in vivo, and the combination will be administered via an intranasal spray. The antiviral therapy will be tested in vivo. If successful, the study will make possible an Investigational New Drug submission to the FDA and could potentially lead to new, more effective options for treatment of upper respiratory tract viral infections.

Dr. Vikhyat Bebarta, University of Colorado, Denver, Programmatic Panel Chair FY19-FY22

"The program 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."

Sgt. 1st Class Daniel McGarrah, Special Operations Command – Central, Programmatic Panel Member FY22

"The CRRP continues to allow a pathway for end-users from the battlefield to pass along their experiences to those researchers looking towards the next conflict and bring innovation to those medical personnel that need it most. All of the military services and Special Operations Command will continue to gain access to the latest medical concepts as CRRP works diligently to eliminate products that do not meet the high standard our Service Members are entitled to. The individuals involved in decision-making processes for the next generation of medical products are building capabilities and limiting our current shortfalls in the medical community across all theaters."

DUCHENNE MUSCULAR DYSTROPHY RESEARCH PROGRAM

Scan me to access even more information about the program.

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

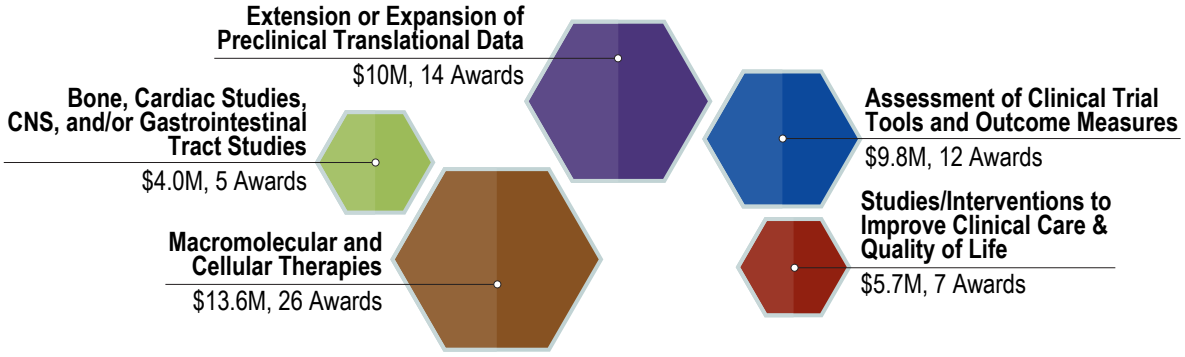
MISSION *To support discovery and development of therapeutics for Duchenne for the benefit of military beneficiaries and the general public, from the characterization of pathophysiology through rigorous preclinical and clinical studies*

PROGRAM HISTORY

Since the inception over the past 11 years since the inception of the Duchenne Muscular Dystrophy Research Program (DMDRP) in 2011, this program has challenged and supported the Duchenne muscular dystrophy (DMD) research community to tackle the difficult questions stemming from therapy development for patients. DMD is the most common childhood form of muscular dystrophy, affecting approximately 1 out of every 5,000 male infants. There is no cure for DMD, and the devastating muscle weakness affecting the skeletal, heart, and respiratory muscles eventually leads to an individual's death before or during their 30s. The DMDRP has received $59.6M in congressional support through FY22, and its current research portfolio of 62 projects includes studies on understanding DMD's effects on 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.

INVESTMENT STRATEGY

With the lack of any curative treatments, the DMDRP has placed its greatest emphasis on developing or improving treatments and clinical trial readiness. Currently, this program focuses its investments in early ideas that address the challenges and opportunities in the development of safe and effective macromolecular and cellular therapies and in advanced translational projects that have moved beyond the realm of basic research and have the potential to result in near-term impact in clinical research or the clinic. The results of DMDRP-funded research are analyzed for their impact in addressing the program's goals, mission, and vision, and the DMDRP revises its investment strategy as needed.



DMDRP Portfolio Investment FY11-FY21

2021 Congressional Appropriations, Research Investment, and Withholds and Management Costs

Congressional Appropriations	*Research Investment*		*Withholds and Management Costs*	
$10M	Idea Development Award – New & Established Investigators	$5,334,705	USAMRDC	$193,340
	Translational Research Award	$3,469,468	SBIR/STTR	$333,000
	Modification to ongoing awards	$8,106	Mgt Costs (6.98%)	$661,382
Total: $10M		**Total:** $8,812,279		**Total:** $1,187,722

EARLY STAGE IDEAS

Muscle-Targeted Cell-Penetrating Peptides for Delivery of Cas9-RNPs and Modified mRNA to Dystrophic Muscle

Dr. Samir El Andaloussi

Explores a new generation vector system based on cell-penetrating peptides to achieve targeted delivery of disease-relevant biotherapeutics Cas9-RNPs and microdystrophin mRNA in DMD in vitro models and in DMD mice.

Novel Therapeutic Strategy to Achieve Upregulation of Dystrophin Isoforms

Dr. Monkol Lek

Design of a CRISPR gene-editing construct to boost dystrophin levels in patients who express residual or low levels of dystrophin. Especially useful for older patients and those with mild DMD.

Targeted Cell-Based Gene Therapies for Persistent Exon Skipping and Dystrophin Restoration in DMD

Dr. James Novak

Explores the potential clinical application of a cell-based gene therapy delivery strategy using macrophages to continuously deliver antisense oligonucleotides to damaged muscle tissue and improve exon skipping therapies.

Irisin and Therapeutics for Duchenne Muscular Dystrophy

Dr. Bruce Spiegelman

Irisin is a natural hormone secreted from muscle that is increased with endurance exercise. Conducting preclinical studies evaluating whether irisin can improve skeletal muscle and cardiac function in DMD mice.

TRANSLATIONAL

MRI Biomarkers of Bone Quality in DMD

Dr. Rebecca Willcocks and Dr. Chamith Rajapakse

Development of magnetic resonance imaging (MRI) measures of bone quality in individuals with DMD as biomarkers for future fracture treatment and fracture prevention clinical trials in DMD. Would provide more accurate assessment of fracture risk as well as evaluation tools for bone-targeted therapeutics.

A Novel Office-Based Injectable to Treat Duchenne-Related Fibrosis

Dr. Benjamin Cooper and Dr. Ara Nazarian

Translation of a novel relaxin-based injectable treatment to mitigate joint contractures due to fibrosis. Project includes all work needed to prepare for human clinical trials for this product.

CLINICAL TRIALS

Impact and Interplay of Corticosteroid Regimen and Exercise Training on DMD Muscle Function

Dr. Tanja Taivassalo and Dr. Warren Dixon

Clinical trial testing two new therapeutic strategies for patients with DMD: a new low-dose weekend regimen of corticosteroids; and a comprehensive exercise training program. The exercise training program includes a new device, Therex-DMD, which allows for therapeutic exercise within the lower extremities for boys living with DMD.

Assessing Arrhythmic Risk in Adult Patients with Duchenne Muscular Dystrophy

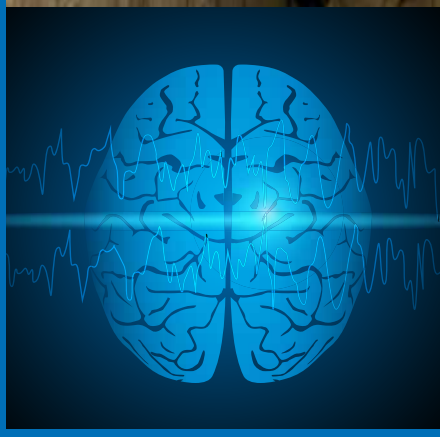
Dr. Andreas Barth and Dr. Natalia Trayanova

Clinical trial to study the natural history of rhythm abnormalities in DMD by implanting miniaturized cardiac monitors in DMD patients at risk for developing potentially life-threatening heart rhythm disorders. A better understanding of arrhythmias could improve patient care by preventing sudden cardiac death.

Jeff Bigelow, Parent Project Muscular Dystrophy, Consumer Peer Reviewer FY20

"Being a member of the review process was exciting. It was invigorating to read research proposals aimed at improving life for my boy and other boys with DMD. It was encouraging to see people dedicating their lives and careers towards making life better for my boy. I know research treatments will be developed to change the life course and day-to-day suffering experienced by my son Henri and other boys with DMD and their families. Great minds are out there, horizons are opening, and this hopeless disease is becoming more hopeful."

EPILEPSY RESEARCH PROGRAM



Scan me to access even more information about the 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

The Epilepsy Research Program (ERP) was initiated in 2015 to support longitudinal epidemiological research to better understand the incidence of post-traumatic epilepsy (PTE) following TBI and to improve patient care and outcomes. Appropriations for the ERP from FY15 through FY21 totaled $61.5M. The FY22 appropriation is $12.0M.

CHALLENGES

In support of the congressional intent of the program, the FY22 ERP challenges the research community to (1) investigate topics related to epileptogenesis for the identification of mechanisms by which brain injury produces epilepsy, (2) study the prevention of PTE and concomitant comorbidities, and (3) develop innovative research tools or biomarkers to better detect, diagnose, or predict the development of PTE.

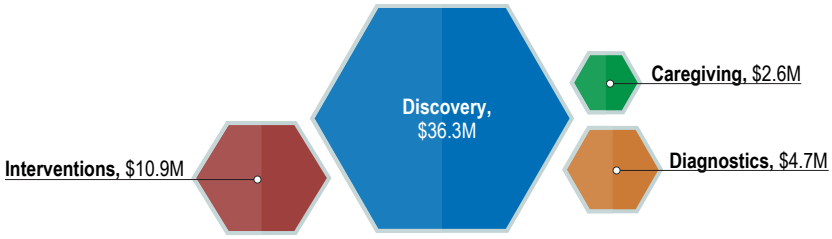
FY22 FOCUS AREAS

Focus Areas are evaluated annually and are used to drive investment into specific program priority areas. The FY22 ERP Focus Areas are:

- **Markers and Mechanisms** – Identifying biomarkers or mechanisms of PTE
- **Epidemiology** – Epidemiological characterization of PTE following TBI
- **Longitudinal Studies** – Studies of the evolution of PTE
- **Innovative Research** – Tools intended to better inform or improve upon PTE research and care

ERP RESEARCH PORTFOLIO

ERP invests heavily into early stage discovery questions related to understanding the fundamentals of PTE, the development of PTE, and the incidence of PTE.

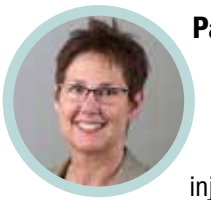


ERP Investment by Scientific Approach FY15-FY21

2021 Congressional Appropriations, Research Investment, and Withholds and Management Costs

Congressional Appropriations	Research Investment	Withholds and Management Costs
$12M	Idea Development Award ..... $7,210,618 Quality of Life Research Award – Funding Level 2 ..... $710,648 Research Partnership Award – Funding Level 1 ..... $2,594,032	USAMRDC ..... $232,000 SBIR/STTR ..... $400,000 Mgt Costs (7.5%) $852,702
Total: $12M	**Total:** $10,515,298	**Total:** $1,484,702

IMPACTFUL RESEARCH OUTCOMES



Patient Self-Reported Medical Histories May Reveal Causes of PTE Beyond TBI Severity

Dr. Mary Jo Pugh, South Texas Veterans Health Care System

FY15 Idea Development Award – While mild traumatic brain injury (mTBI) represents a significant portion of TBI injuries sustained by Veterans, it is poorly documented and tracked in health records, making it difficult to understand mechanisms of injury and outcomes for subsequent complications, such as PTE. This novel study compares self-reported lifetime history to medical diagnoses of TBI in a post-9/11 Veteran cohort, a population with high mTBI incidence. Initial findings reinforce that persons with epilepsy in addition to TBI have worse physical functioning and quality of life than those with either epilepsy or TBI alone.

Can Negative Neurological Outcomes from Mild Repetitive TBI be Prevented by Blocking TGFβ?

Dr. Alon Friedman, Dalhousie University

FY16 Idea Development Award – Repetitive mTBI (rmTBI) results in loss of consciousness and a wide range of hazardous, long-term neurological problems, but there are still no known biomarkers to predict patient outcomes after injury. Based on work from this study, the research team found the activity of a protein known as transforming growth factor β (TGFβ), which participates in inflammatory signaling, increased after rmTBI in their rat model. Blocking the activity of this protein with a selective inhibitor reduced neurobehavioral complications after injury, suggesting this protein may be associated with these severe, potentially life-threatening consequences of rmTBI.

Differences in Gut Bacteria Prior to TBI May Predict Development of PTE

Dr. Andrey Mazarati, University of California, Los Angeles

FY18 Idea Development Award – The gut-brain axis is linked to several disorders such as depression, anxiety, autism, Alzheimer's disease, and Parkinson's disease, but more recent data also implicates symptoms of several other neurological disorders, including stroke, TBI, and epilepsy. The research team in this study analyzed the gut bacteria of rats that either did or did not develop PTE following TBI, and they identified four types of bacteria and several bacterial products associated with the risk of developing PTE. This study sheds light on how the composition of the pre-injury gut microbiome may modulate susceptibility to PTE and make it possible to identify people most at risk of PTE development.

NEW PROJECTS FOR FY21

Identification and characterization of altered brain activity, neuroinflammation, and degeneration following multiple blast exposures – ***Walter Reed Army Institute of Research – Idea Development Award***

Neuroimaging to identify abnormal structural network profiles in the brain following TBI paired with machine learning to predict PTE – ***University of Pennsylvania – Idea Development Award***

Integrating psychosocial care with standard neurology interventions to better manage anxiety and/or depression among adults with PTE – ***Wake Forest University Health Sciences – Quality of Life Research Award***

MILITARY INJURIES & UNDERSTANDING POST-TRAUMATIC EPILEPSY: THE MINUTE STUDY

Dr. Mary Jo Pugh of the University of Utah leads the MINUTE study, an ERP-funded effort examining health and quality of life for post-9/11 Veterans with and without PTE as well as their caregivers. The goals of this study are to identify available support and unmet needs to help define characteristics associated with health trajectories in Veterans living with PTE. – *FY19 Research Partnership Award and FY20 Research Partnership Award*

Alison Zetterquist, Epilepsy Foundation, Consumer Peer Reviewer FY20-FY21

"I've had the honor of being an ERP consumer reviewer twice, and I have to say that they've been among my most fulfilling endeavors in recent years. The Department of Defense is a significant source for epilepsy research funding and, not being a scientist myself, being able to serve as a consumer reviewer has made me feel that I'm doing my part to help access it alongside the experts. Knowing that the scientist would be able to evaluate the research rigor, I was able to focus on critical patient-centered expertise."

HEARING RESTORATION RESEARCH PROGRAM

Scanning electron micrograph of a stereoclia bundle on the apical surface of a human pluripotent stem cell-derived hair cell.* Magnification: x10,000

**Image Courtesy of Dr. Eri Hashino, Indiana University*

Scan me to access even more information about the 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 established the Peer Reviewed Hearing Restoration Research Program (HRRP) in 2017 to pursue regenerative strategies and other options that reduce the burden of hearing loss among Service Members.

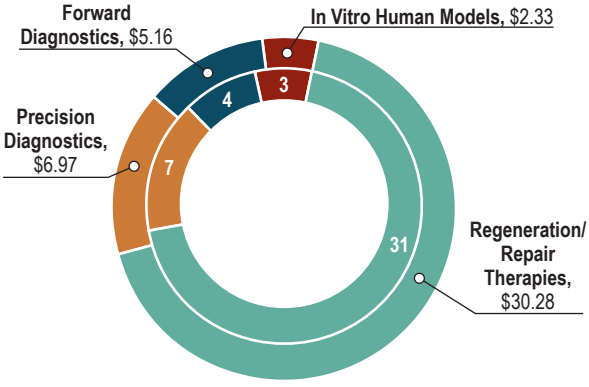
Disabling hearing loss affects more than 30 million Americans, including over 1.3 million Veterans. While hearing loss has profound impact on quality of life, there is no drug approved by the FDA for hearing restoration. The development of hearing restoration therapeutics has been hindered by difficulties in the validation/translation of preclinical findings and limitations in precision diagnostic capability. The HRRP aims to advance the science of hearing restoration by funding groundbreaking research that removes barriers to translation and diagnosis.

RELEVANCE TO MILITARY HEALTH

Service Members face high risks of auditory system injury from extended exposure to combat and operational noise such as gunshots, explosions, helicopters, etc. Protection against combat noise is complicated by its unpredictable nature and by the need for Warfighters to communicate and to listen/respond to sounds. Furthermore, Service Members often operate in austere/remote environments where diagnostic and treatment resources and medical personnel are unavailable or limited for extended periods of time. To improve military auditory health, the HRRP addresses both diagnosis and mitigation of auditory system injury.

FOCUS AREAS

- Regeneration/Repair Therapies
- Precision Diagnostics
- In Vitro Human Models
- Forward Diagnostics



HRRP Funding (Millions) and Awards by Focus Area FY17-FY21

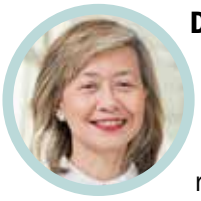
2021 Congressional Appropriations, Research Investment, and Withholds and Management Costs

Congressional Appropriations	*Research Investment*	*Withholds and Management Costs*
$10M	Focused Research Award – Funding Level 1 ..... $1,140,361 Focused Research Award – Funding Level 2 ..... $8,078,036 Modification to ongoing awards $3,500	USAMRDC ..... $193,340 SBIR/STTR ..... $333,000 Mgt Costs (2.66%) $251,763
Total: $10M	**Total:** $9,225,397	**Total:** $778,103

CDMRP and NIDCD Host Joint Workshop on Ex Vivo Models

The CDMRP and the National Institute on Deafness and Other Communication Disorders (NIDCD) co-hosted a virtual workshop in November 2021 to encourage the enhancement of ex vivo models and techniques to expedite translation of hearing loss therapies. The workshop consisted of focused sessions on ear organoids, organoids of other organs, and enabling technologies, all aimed at accelerating the development, validation, and clinical throughput of hearing loss therapies. Dr. Debara Tucci, director of NIDCD, and Col. Sarah Goldman, director of CDMRP, noted the importance of the research and collaboration between the two organizations. Following the presentations, speakers and attendees participated in discussions on the opportunities and challenges associated with ex vivo models and possible steps needed to fulfill the promise of these approaches.

RECENT ACHIEVEMENTS FROM HRRP-FUNDED RESEARCH



Directed Differentiation of Human Pluripotent Stem Cells into Inner Ear Organoids[1]

Dr. Eri Hashino, Indiana University-Indianapolis

Evaluating pharmaceutical treatments for inner ear hair cell regeneration is limited by the lack of in vitro cell culture systems that mimic the inner ear. Funded by an FY17 TRA, Dr. Eri Hashino and team are growing human inner ear organoids in a three-dimensional format that represents the structure and function of human inner ear tissues. Published in *Methods in Molecular Biology*, the team has successfully developed a protocol to use human pluripotent stem cells to generate these organoids containing sensory epithelia with hair cells. This protocol provides a platform for further research in the human inner ear, including a model system to discover therapeutic targets for hearing restoration.

Miniature Imaging Probe to Visualize Cellular Pathology in the Inner Ear[2]

Dr. Konstantina Stankovic, Stanford University

Damage to cells or cellular structures in the inner ear is a leading cause of hearing loss. Coiled into a few millimeters in diameter and encased in hard bones, the inner ear is difficult to access and examine, creating a tremendous hurdle for matching potential therapeutics to the correct patients and evaluating therapeutic effects. With funding from an FY19 Focused Research Award, a team led by Dr. Konstantina Stankovic and Dr. Guillermo Tearney developed a sub-millimeter-diameter, flexible endomicroscopic probe to image cellular structures in the inner ear at micron-scale resolution. The probe holds great promise for in vivo examination of inner ear pathology, a missing yet crucial piece in the puzzle of sensorineural hearing loss therapeutic development and clinical trials. Its potential clinical applications also include real-time guidance of cochlear implantation, thus improving the positioning of implant electrode arrays and hearing outcomes in implant patients.

Hair Cell Regeneration in Cultured Adult Cochlea[3]

Dr. Zheng-Yi Chen, Massachusetts Eye and Ear Infirmary

Dr. Zheng-Yi Chen received an FY17 Translational Research Award to study molecular mechanisms of hair cell regeneration to promote hearing restoration after noise-induced hearing loss. As recently published in *Frontiers in Molecular Neuroscience*, the research team established a new system to culture adult mouse cochlea with the surrounding bone to maintain the overall structure. Using the explant system, they showed that the cochlear supporting cells can be reprogrammed by Atoh1 to become hair cell-like cells, which are able to make contact with neurons. These advancements will allow researchers to study the inner ear in vitro to understand how to promote functional regeneration of cochlear tissue.

Christina Becude, Vestibular Disorders Association, Consumer Peer Reviewer FY21-FY22

"The intricacies of hearing loss are so complex and oftentimes frustrating. Being a consumer reviewer for the Hearing Restoration Research Program was an honor and eye-opening experience, serving alongside the brilliant scientists in reviewing the multi-faceted research programs that seek to discover therapies, enhancement of listening devices, as well as discovering a cure for hearing loss. Having lost my hearing at a very young age, I was honored the scientists listened to and appreciated my input as a consumer. Being a part of the process gives me hope that this crucial research will provide different avenues of relief one day to those who suffer from hearing loss!"

Jack King, Vestibular Disorders Association, Consumer Peer Reviewer FY19-FY21

"I would just say that I'm delighted to have had the opportunity to serve with HRRP these past few years. It is rewarding to know that I am playing a role in guiding the future of hearing research that can help others with hearing loss, especially Soldiers who have given up much for our country. I look forward to each year's committee because I enjoy meeting and interacting with other wonderful people who are like-minded!"

References: [1] doi: 10.1007/7651_2021_448. | [2] doi: 10.1038/s41598-021-95991-8. | [3] doi: 10.3389/fnmol.2021.757831.

JOINT WARFIGHTER MEDICAL RESEARCH PROGRAM

Scan me to access even more information about the 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

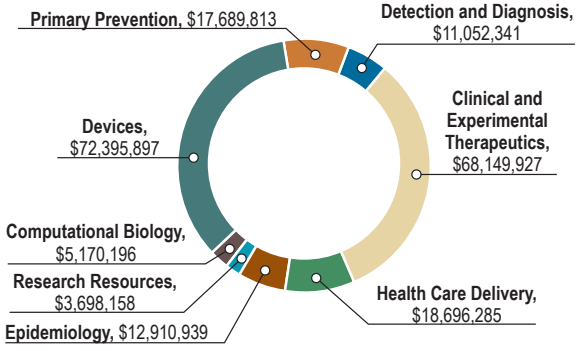
MISSION

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

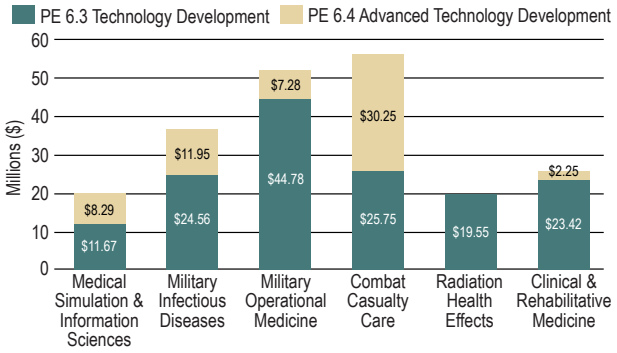
PROGRAM HISTORY

The Joint Warfighter Medical Research Program (JWMRP) was initiated in FY12 to provide a way to continue Warfighter-relevant medical research and development projects that had been previously funded with DOD Congressional Special Interest dollars. The program was expanded by Congress in FY18 to include continuation of projects with prior DOD core program funding as well. JWMRP funds are not to be used for new projects or for basic research. The JWMRP leverages the efforts of industry, academia, and DOD laboratories to augment and accelerate projects that show promise in closing high-priority joint- and service-specific DOD medical requirements and capability gaps to move products across the "valley of death," toward advanced development, to get products to the Warfighter faster and better. The program coordinates with USAMRDC leadership, including the JPCs, as well as the U.S. Army Medical Materiel Development Activity (USAMMDA) Project Management Offices, Navy, Air Force, Special Operations Command, and the Defense Health Agency to identify priority areas each year.

Congressional appropriations for the JWMRP total $570M to date. A total of 270 JWMRP awards have been made from FY12-FY21, funding 170 individual projects. JWMRP projects align to various military medical research areas, including Military Infectious Diseases, Military Operational Medicine, and Combat Casualty Care. By focusing on both early and advanced technology development, the JWMRP provides a pathway to transition military medical products to military health care providers and the Warfighter.



JWMRP Investment by Research Type FY17-FY21



JWMRP Funding Distribution FY17-FY21

2021 Congressional Appropriations, Research Investment, and Withholds and Management Costs

Congressional Appropriations	*Research Investment*	*Withholds and Management Costs*
$40M	Military Medical Research and Devleopment Award ..... $33,085,940 Modification to ongoing awards $1,543,567	USAMRDC ..... $773,300 SBIR/STTR ..... $1,335,000 Mgt Costs (8.61%) $3,262,192
Total: $40M	**Total:** $34,629,507	**Total:** $5,370,492

Technology Readiness Level

4

Novel MRI quantification of cervical and lumbar spine kinematics in swift boat Combatant Crewmen

Wearable spine health system for military readiness assessment

MeniscoFix total meniscus replacement device

5

Phase 1/2 clinical trial of bacteriophage for treatment of bacterial infections

AccuPump™ infusion pump module for the delivery of drugs, fluids, and blood products at point of injury

Phase 1 clinical trial of Vital Wave non-contact vital signs monitor

PleuraPath™ chest tube for thoracostomy

Multi-site clinical trial of a neural-enabled prosthetic hand system

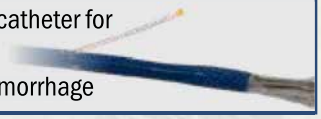
Phase 1 clinical trial for therapeutic intervention particles as an antiviral against HIV

6

Ultrasound for assessing critical head trauma

Multicenter implementation trial of targeted normoxia strategy to inform oxygen requirements for combat casualty care

Thrombopoietin mimetic to prevent/mitigate acute radiation syndrome



Resuscitative Endovascular Balloon Occlusion of the Aorta physiologic sensing catheter for advanced control of noncompressible torso hemorrhage

8

Phase 3 clinical trial of Sanaria PfSPZ vaccine in malaria-naive adults

Autonomous portable blood refrigeration unit as a battlefield whole blood logistics solution

Eddie C. Webb, Medical Research and Acquisition Program Management Branch, Programmatic Panel Member FY20-FY22

"Since 2012, the JWMRP has augmented Department of Defense and Service Component efforts to develop materiel products to meet medical Warfighter requirements. It has provided the Air Force Medical Service an opportunity to bring solutions forward more expeditiously – both for existing initiatives close to achieving their objectives and for emerging materiel acquisition programs applicable to the joint community. Sponsored efforts encompass medical device development integral to the Combatant Commander interests. The JWMRP program is a powerful tool in advancing medical product development to support DOD capabilities."

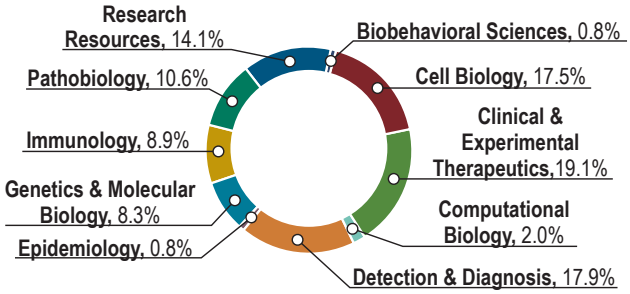
KIDNEY CANCER RESEARCH PROGRAM

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

The DOD Peer Reviewed Kidney Cancer Research Program (KCRP) was established in 2017 as a result of efforts by kidney cancer advocates and the support of Congress. The KCRP has received $185M in congressional appropriations through FY22. Through offering and funding more than 196 research awards, 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.



KCRP Portfolio Investment by Research Type FY17-FY21

RELEVANCE TO MILITARY HEALTH

Tobacco smoking and 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 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.

Scan me to access even more information about the program.

MILITARY HEALTH SYSTEM DATA

Individuals with kidney cancer may require extensive treatment of patient services; as such, this is relevant to the military. Approximately ***51,000*** new cases were reported within the MHS between 2010 and 2019, with ***911*** active-duty Service Members diagnosed with kidney cancer. These individuals endured a total of ***6,176*** outpatient encounters, resulting in ***2,046*** hospital bed days.

[1] McLaughlin JK, Hrubec Z, Heineman EF, et al. 1990. Renal cancer and cigarette smoking in a 26-year followup of U.S. veterans. *Public Health Rep* 105: 535-537.
[2] Saint-Jacques N, Parker L, Brown P, and Dummer TJ. 2014. Arsenic in drinking water and urinary tract cancers: A systematic review of 30 years of epidemiological evidence. *Environ Health* 13:13-44.
[3] Saint-Jacques N, Brown P, Nauta L, et al. 2018. Estimating the risk of bladder and kidney cancer from exposure to low levels of arsenic in drinking water, Nova Scotia, Canada. *Environ Health* 110:95-104.

2021 Congressional Appropriations, Research Investment, and Withholds and Management Costs

Congressional Appropriations	*Research Investment*	*Withholds and Management Costs*
$50M	Academy of Kidney Cancer Investigators – Early Career Investigator Award ..... $2,479,500 Clinical Trial Award ..... $6,699,994 Concept Award ..... $1,258,111 Idea Development Award ..... $14,859,934 Postdoctoral and Clinical Fellowship Award ..... $2,351,066 Translational Research Partnership Award ..... $10,357,873 Modification to ongoing awards $6,842,491	USAMRDC ..... $875,575 SBIR/STTR ..... $1,668,000 Mgt Costs (5.49%) $2,607,455
Total: $50M	**Total:** $44,848,970	**Total:** $5,151,030

FOCUS AREAS

- Basic biology research to better understand kidney cancer
- Screening, early-stage detection, and accurate diagnosis and prognosis prediction of kidney cancers
- Biology of rare kidney cancers
- Novel therapeutic strategies for the treatment of kidney cancer
- Strategies to improve the quality of life and survivorship for patients
- Strategies to mitigate health disparities
- Support next generation of kidney cancer researchers or cultivate collaborations in kidney cancer research

RESEARCH HIGHLIGHTS

First Functional Analysis of an Inherited SETD2 Mutation Associated with Renal Cell Carcinoma

Dr. Rebecca S. Arnold, Emory University

Dr. Arnold received a KCRP FY18 Concept Award to study links between an inheritable mutation of the tumor suppressor gene SETD2 and kidney cancer occurrence by developing Drosophila fruit fly models and studying functional effects of genetic modifications. Dr. Arnold's team demonstrated that a single amino acid point mutation that was more commonly found in kidney cancer patients resulted in molecular and cell biologic effects. Continuation of this research may potentially yield a genetic risk factor screening tool.

Is VISTA:VSIG3 an Actionable Immune Checkpoint Target in Kidney Cancer?

Dr. Kathleen Mahoney, Dana-Farber Cancer Institute

Cancer patients that do not respond to PD-1 blockade immunotherapy may have other anti-tumor immune response pathways activated, such as immune checkpoint regulator VISTA, which is highly expressed in several kidney cancers. The acidity of the tumor microenvironment also alters immune response. With support from a KCRP FY18 IDA, Dr. Mahoney's preliminary results show promise that PSGL-1 can block VISTA under acidic environments while VSIG3 can block VISTA under neutral environments, suggesting that the PSGL1:VISTA pathway may be a critical player in tumor environments.

Genomic and Functional Analysis of Translocation Renal Cell Carcinoma

Dr. Srinivas R. Viswanathan, Dana-Farber Cancer Institute

Dr. Viswanathan was awarded a KCRP FY18 IDA to study the biology of rare and aggressive kidney cancer subtype translocation renal cell carcinoma (TRCC). Dr. Viswanathan's team completed whole genome sequencing and found that TRCC's genomic landscape is fairly homogenous, with low occurrence of deviation from the characteristic MiT/TFE fusions and specific 9p21.3 deletions. Further, it transcriptionally shows increased expression of NRF2, which could play a role in resisting targeted therapies.

A Nested Case-Control Study of Serum Levels of Polyfluoroalkyl Chemicals (PFCs) and Kidney Cancer Among Participants in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial

Dr. Jonathan Hofmann, National Cancer Institute

Dr. Hofmann and team, with support from a KCRP FY17 Concept Award, studied pre-diagnosis blood serum of renal cell carcinoma patients for association between exposure to eight different common industrial chemicals, such as through cookware, textile, and/or firefighting foam, and kidney cancer occurrence. Dr. Hofmann's team confirmed that evidence shows perfluorooctanoic acid can be considered a renal carcinogen.

Targeting Resistance Mechanisms in SMARCB1-Deficient Tumors

Dr. Giannicola Genovese and Dr. Pavlos Msaouel, M.D. Anderson Cancer Center

Inactivation of SMARCB1 gene leads to various types of rare and aggressive kidney cancers, including renal medullary carcinoma (RMC) and malignant rhabdoid tumors (MRT). Drs. Genovese and Msaouel are currently running a clinical trial testing their targeted therapy that utilizes proteasome inhibitors to treat RMC and MRT; however, patients eventually develop resistance. Leveraging patient samples collected from this clinical trial, the team was awarded with a KCRP FY20 Translational Research Partnership Award to study the mechanism behind the development of proteasome inhibitor resistance in SMARCB1-deficient patients.

Cora Connor, RMC Support, Programmatic Panel Member FY21

"My experience as a programmatic reviewer was invaluable. I was able to share information from a caregiver and advocate standpoint. It gives the rare disease community hope, knowing that there are passionate scientists and researchers who are making a difference in their lives."

LUNG CANCER RESEARCH PROGRAM

Scan me to access even more information about the program.

VISION

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

MISSION

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

PROGRAM HISTORY

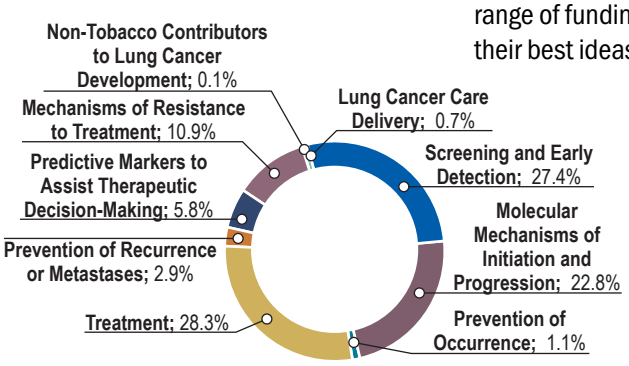
Over the past 13 years, since the inception of the Lung Cancer Research Program (LCRP) in 2009, this program has received $195.5M in congressional support. The LCRP has played a critical role in helping to accelerate high-impact translational research, encourage innovation and stimulate creativity, bring new investigators into the lung cancer field, and facilitate the creation of unique partnerships and resources. The program has fostered the development of over 75 new investigators, and it currently supports five clinical trials exploring innovative approaches to detection and treatment.

LUNG CANCER RELEVANCE TO MILITARY HEALTH

Lung cancer risk for our military is significant, as 24% to as high as 38% of Service Members are smokers[1] and an estimated 900,000 Veterans remain at risk due to age, smoking, and other environmental exposures during and after military service. From 2010 to 2019, there were over 2.7 million outpatient encounters and more than 450,000 hospital bed days for lung cancer by DOD beneficiaries.[2]

INVESTMENT STRATEGY

The LCRP recognizes there is a broad range of research questions that are critical to advancing prevention, detection, treatments, and cures for lung cancer. A wide range of funding mechanisms are offered that enable investigators to propose their best ideas and further high-impact, innovative lung cancer research focused on underfunded and underrepresented areas. To meet this substantial need, the LCRP has identified Areas of Emphasis (AoE) to address both the scientific and consumer communities. The program continuously analyzes the outcomes of LCRP-funded projects to assess progress in addressing the AoEs, mission, and vision, and revises the investment strategy as needed.



LCRP Dollars Invested per Area of Emphasis FY09-FY21

[1] U.S. Secretary of Defense. 2016. Memorandum for secretaries of the military departments. Washington, DC: U.S. Secretary of Defense.
[2] Data provided by the Armed Forces Health Surveillance Branch based on electronic records within the Defense Medical Surveillance System.

2021 Congressional Appropriations, Research Investment, and Withholds and Management Costs

Congressional Appropriations	*Research Investment*	*Withholds and Management Costs*
$20M	Career Development Award ..... $1,204,436 Clinical Translational Research Partnership Award ..... $3,772,545 Concept Award ..... $2,043,493 Expansion Award ..... $633,000 Idea Development Award – New & Established Investigators ..... $6,613,153 Investigator Initiated Translational Research Award ..... $3,742,874 Modification to ongoing awards $25,998	USAMRDC ..... $386,660 SBIR/STTR ..... $667,000 Mgt Costs (4.81%) $910,841
Total: $20M	**Total:** $18,035,499	**Total:** $1,964,501

PROMISING RESEARCH ALONG THE CANCER CARE SPECTRUM

Area of Emphasis	Research Highlights
Biology/Etiology	
Molecular Mechanisms of Initiation and Progression	 **Specific Targeting of the TACE Protease as a Therapeutic Strategy in Lung Adenocarcinoma and Associated Cachexia** ***Dr. Brendan Jenkins, Monash University*** With funding from LCRP, Dr. Jenkins' team confirmed in mouse models that TNFα-converting enzyme (TACE) plays a key role in promoting mutant KRAS-driven and tobacco smoke carcinogen-driven lung adenocarcinoma development. The team also tested various TACE inhibitors in vivo and found a less toxic recombinant candidate to elicit anti-cancer effects; they are hopeful that a TACE inhibitor could be a therapeutic option for KRAS-driven and tobacco smoke-associated lung cancer.
Mechanisms of Resistance to Treatment	 **Tumor Heterogeneity and Therapeutic Resistance in Small Cell Lung Cancer (SCLC)** ***Dr. Lauren Byers, University of Texas*** Resistance to the available treatments for SCLC is common and generally develops rapidly. Through the support of an LCRP FY17 Idea Development Award, Dr. Byers' research team molecularly identified and characterized four subtypes of SCLC and aligned them to different therapies that optimize response. The team speculates that cells potentially shifting from one to another subtype could lead to platinum and PAPRi treatment resistance. With support from an FY21 LCRP Expansion Award, the team will continue their study on tumor heterogeneity and drug resistance on a cellular level.
Prevention	
Prevention of Occurrence	 **A Novel Agent for Lung Cancer Prevention** ***Dr. Arun Sharma, Pennsylvania State University*** Using preclinical smoking-induced lung cancer mouse models, Dr. Sharma and his team elucidated promising data suggesting that a conjugated 1,4-phenylenebis(methylene)-seleconcyanote and aspirin (p-XS-Asp) compound effectively prevented lung cancer development at both the peri-initiation and post-initiation stages. Work is ongoing to understand the molecular mechanism underlying this intervention.
Detection, Diagnosis, Prognosis	
Predictive Markers to Assist Therapeutic Decision-Making	 **Noninvasive Imaging of Mitochondria Structure and Function to Predict Therapeutic Response in NSCLC** ***Dr. David Shackelford, University of California, Los Angeles*** Seeking to improve the diagnosis and treatment of non-small cell lung cancer (NSCLC), Dr. Shackelford and his team developed a novel positron emission tomography tracer 18F-bnTP probe (FTP) for imaging mitochondrial structure and function in lung tumors. The team found the mitochondrial length, mitochondrial membrane potential, and FTP uptake into tumor cells is inversely correlated to the amount of treatment uptake and cell viability in NSCLC cell and mouse models, and therefore could be predictors of chemotherapy response. The team will continue to advance these studies and investigate mitochondrial structure regulators.
Treatment	
Treatment	  **Targeting ART1, a Novel Immune Checkpoint, for the Treatment of Lung Cancer** ***Dr. Brendon Stiles, Albert Einstein College of Medicine/Montefiore*** ***Dr. Timothy McGraw, Cornell University*** ART1 is suggested to play a role in lung cancer progression. With funding from the LCRP, Drs. Stiles and McGraw are evaluating the use of therapeutic monoclonal antibodies for ART1 inhibition in mouse models. Initial results show promise in significantly decreasing tumor burden, leading to communications with a company to potentially further develop the anti-ART1 antibodies as an immunotherapy treatment and in combination with radiation therapy for the treatment of NSCLC. Work is continuing, as the team is evaluating ART1 expression, signaling, and immune composition in VA-based NSCLC patients receiving pre-operative immune checkpoint blockade and radiation therapy.

Elizabeth de Jong, Cancer Support Community, Consumer Peer Reviewer FY19-FY21

"Serving as a voice for the lung cancer community among scientific reviewers is a responsibility that I take seriously. I want to be able to share the patient perspective with care providers, scientists, and researchers at the table – to let them see the people behind the diagnosis, the treatments, and the research. Of all of the advocacy, fundraising, and education I have done related to lung cancer, serving as a Consumer Reviewer for the LCRP is the most challenging and the most rewarding."

LUPUS RESEARCH PROGRAM

Scan me to access even more information about the program.

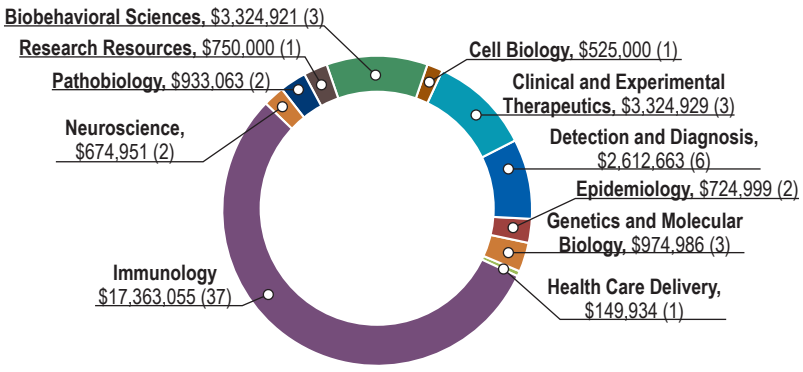
VISION *To cure lupus through partnership of scientists, clinicians, and consumers*

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

Lupus research was first funded by the CDMRP as a Topic Area in the Peer Review Medical Research Program (PRMRP). From FY05-FY16, the CDMRP funded 21 lupus research awards for a total of $20.6M. The Lupus Research Program (LRP) was initiated in 2017 to provide support for innovative and impactful research of exceptional scientific merit that addresses significant issues and gaps in lupus knowledge. Appropriations for the LRP from FY17 through FY21 totaled $35M. For FY22, the Defense Appropriations Act provides $10M to the LRP to support innovative and impactful research that addresses significant issues in lupus. Thus far, 60 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. Currently, no test is 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, and long-term use of these treatments can result in serious side effects. Better treatment options are a critical need for lupus patients.



LRP Portfolio by Research Type (Number of Awards) FY17-FY21

2021 Congressional Appropriations, Research Investment, and Withholds and Management Costs

Congressional Appropriations	*Research Investment*		*Withholds and Management Costs*	
$10M	Idea Award	$1,498,944	USAMRDC	$193,340
	Impact Award	$5,248,864	SBIR/STTR	$333,000
	Transformative Vision Award – Clinical Trial	$2,499,921	Mgt Costs (2.38%)	$225,931
Total: $10M		**Total:** $9,247,729		**Total:** $752,271

Clarifying Mechanisms of Treg Function as a Basis for SLE Therapy

Dr. Charles Fathman, Stanford University School of Medicine

Dr. Charles Garrison (Garry) Fathman, M.D., Stanford University School of Medicine, received an award from the CDMRP's Lupus Research Program. The award is titled, "Identification, Characterization, and Correction of a Defect in Treg Function in SLE."

Regulatory T cells (Tregs) maintain self-tolerance, and a loss of Treg function contributes to the development of various autoimmune diseases, including systemic lupus erythematosus (SLE). The Principal Investigator's (PI) laboratory previously identified a druggable defect in the Tregs of patients with SLE. Dr. Fathman's lab showed that the Tregs of SLE patients express reduced levels of a protein, GRAIL, which is essential to Treg function. In healthy individuals, GRAIL inhibits desensitization of the IL-2 receptor (IL-2R) in Tregs to support transcription of the genes required for Treg function. Reduced GRAIL expression in SLE patients results in a loss of IL-2 activity via diminished inhibition of IL-2R desensitization and, ultimately, diminished Treg function and loss of self-tolerance (autoimmunity).

The project extends previous findings of Dr. Fathman's work by examining the role of Tregs in SLE. His studies will test the hypothesis that most SLE patients have a common defect in their Tregs (GRAIL deficiency) and that the defect in IL-2R signaling and Treg function can be repaired using a human thioredoxin/IL-2 fusion protein drug conjugate to deliver a small molecule drug to restore GRAIL's function.

The aims of the award are to develop an assay that can identify the subset of SLE patients that have a defect in Treg function and to develop a treatment that can repair the IL-2R signaling defect in their Tregs. This treatment will enhance or restore Treg function and self-tolerance in SLE patients. Successful completion of the award's aims will represent a paradigm shift in therapy in which autoimmune diseases are treated by the restoration of immune tolerance rather than using immunosuppressive drugs to inhibit inflammatory effector cells.

Link:
Public and Technical Abstracts: Identification, Characterization, and Correction of a Defect in Treg Function in SLE

Therapeutic Targeting of Senescent Cells in Lupus

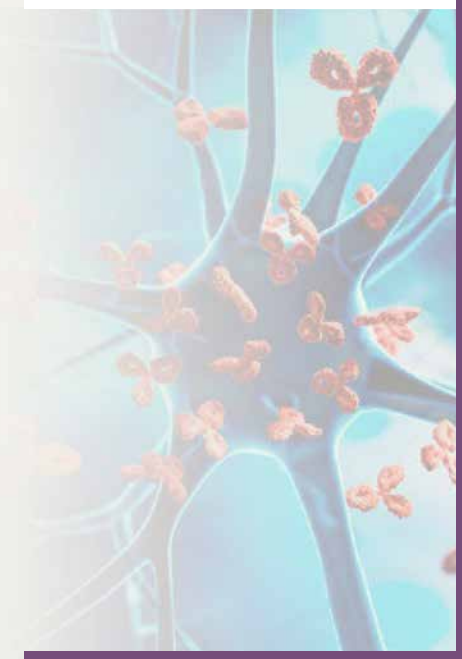
Dr. Richard Looney, University of Rochester Medical Center

Drugs that target senescent cells (senolytic drugs) are used to rejuvenate tissues and have the potential to improve kidney function in patients with renal disease. Senescent cells are abnormal cells that can interfere with the normal functions of surrounding cells. Many senolytic drugs are already approved for human use, and many cells expressing senescence have been identified in other types of chronic kidney disease; however, these studies did not include patients with lupus. Dr. Looney aimed to evaluate the accumulation of senescent cells in lupus target tissue and discover if the senescent cells can be targeted by existing senolytic drugs. To assess, a variety of senolytic drugs were tested in vitro (in a test tube) on BM-MSC from SLE patients and from lupus model (NZB/W) mice. The kidney tissue of SLE patients and NZB/W mice was also examined for markers of senescence. Dr. Looney and his team's findings suggest that use of senolytic drugs in lupus may selectively eliminate senescent cells in kidneys and other tissues. The research team hopes that senolytic drugs can be used to change this treatment paradigm and improve the quality of life for individuals with SLE.

Link:
Public and Technical Abstracts: Therapeutic Targeting of Senescent Cells in Lupus

Dr. Timothy Niewold, Hospital for Special Surgery, Programmatic Panel Member FY17-FY22

"The DOD Lupus Research Program supports vital needs of the lupus research community, as we work to provide new solutions for patients with this debilitating autoimmune disease. The Idea and Impact Awards support novel 'out-of-the-box' ideas in their early stages to allow for path-breaking research, and the Transformative Vision Awards provide substantial support that can bring new solutions toward the clinic. This program is vital to our continued progress in understanding and treating lupus."



Linda Ridpath, Lupus Foundation of America, Consumer Peer Reviewer 2014, 2016-2018, 2021

"I have been honored to add my voice to the LRP community. The experience has left me feeling both empowered and hopeful. I believe that the science is making a definable and positive difference in the future of the lives of the lupus patient."

MELANOMA RESEARCH PROGRAM

Scan me to access even more information about the 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 2022, it is estimated that 99,780 new cases of melanoma of the skin in the U.S. will be diagnosed, a 1.2% increase in new cases since 2021. 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.

FY22 MRP CHALLENGE STATEMENT

The MRP challenges the research community to prevent melanoma initiation and progression. The clinical, research, and patient communities traditionally view prevention as the use of sunscreen/blockers to protect melanocytes from harmful ultraviolet (UV) radiation. The MRP tasks the research community to redefine prevention to include the entire melanomagenesis process for all variants of melanoma. A new paradigm of prevention includes improved detection and monitoring capabilities, as well as inhibiting the initiation of melanoma, the emergence from tumor dormancy, and the development of metastases. The MRP believes the research community can rise to the challenge to inhibit melanoma earlier in the disease progression to prevent metastasis and increase survival.

MRP FOCUS AREAS

2021 Congressional Appropriations, Research Investment, and Withholds and Management Costs

Congressional Appropriations	*Research Investment*		*Withholds and Management Costs*	
$30M	Discovery Award	$2,863,740	USAMRDC	$562,243
	Idea Award	$9,969,869	SBIR/STTR	$1,000,000
	Melanoma Academy Leadership Award	$2,144,998	Mgt Costs (4.77%)	$1,356,763
	Melanoma Academy Scholar Award	$1,279,014		
	Mid-Career Accelerator Award	$4,774,668		
	Team Science Award	$4,092,958		
	Translational Research Award	$1,955,747		
Total: $30M		**Total:** $27,080,994		**Total:** $2,919,006

MRP - INVESTING IN PREVENTION

FY19 Focus Area: Therapeutic Prevention	Concept Award

Targeting the Oncoprotein RLIP as Novel Therapy for Melanoma

Dr. Sharad S. Singhal, City of Hope National Medical Center, Beckman Research Institute

Melanocyte exposure to UV radiation can generate cellular oxidative stress that results in DNA damage and melanoma formation. Dr. Singhal is studying RLIP, an anti-apoptotic (prevents cancer cell death) membrane transporter that serves a critical role in regulating cellular oxidative stress and is over-expressed in melanoma. His findings to date show that RLIP inhibition prevents the formation of melanoma in a cell-based model, and that therapeutic depletion of RLIP in a mouse model results in melanoma regression. These results may pave the way for much-needed novel therapeutic preventatives and/or treatment options for melanoma.

FY19 Focus Areas: 1. Precursor Lesions, Melanomagenesis, Host Factors, and the Tumor Microenvironment 2. Therapeutic Prevention	Translational Research Award

Role of LILRB4 in Melanoma

Dr. Chengcheng Zhang, University of Texas, Southwestern Medical Center at Dallas

There is a need for novel immunotherapy targets since not all patients benefit from the currently approved immunotherapies. One possible new target is LILRB4, a protein expressed on the surface of certain white blood cells that may regulate cancer growth and relapse. The goal of Dr. Zhang's proposal is to elucidate the molecular mechanisms that drive the expression and function of LILRB4 and determine whether targeting LILRB4 is a valuable strategy for melanoma treatment. The success of this study could lead to clinical trials that may combine immunotherapy and targeted therapy.

FY20 Focus Area: Prevention of Melanomagenesis and Precursor Lesions	Mid-Career Accelerator Award

Understanding Transition from Nevi to Melanoma Occurring Within the Skin Epidermis

Dr. Mayumi Ito, New York University School of Medicine

Clinical studies suggest that a large percentage of cutaneous melanomas arise from the malignant transformation of benign nevi (i.e., moles), but the mechanism driving this transformation is not well-understood. Using a novel mouse model developed by her laboratory, Dr. Ito aims to provide the first detailed map of this process and test whether established immunotherapeutic drugs could be used to prevent melanoma formation and/or progression. Future studies could exploit these results to identify the minimal dosages of drugs or combinations of drugs that may prevent melanoma.

J.B. Ward, AIM at Melanoma, Consumer Peer Reviewer FY19-FY22

"Working with the MRP has been an incredibly rewarding opportunity to meet and interact with top researchers in the field, be one of the first people to view up-and-coming melanoma research ideas, and, at times, advocate for patients when there are concerns about an application. Serving as a Consumer Peer Reviewer for the MRP has proven to be a wonderful fit for me and my desire to continue fighting for improved outcomes for people diagnosed with melanoma and to find answers for the many unknowns in mucosal melanoma."

TYPES OF MELANOMA

- Cutaneous
- Acral
- Pediatric
- Ocular
- Mucosal
- Leptomeningeal

MILITARY BURN RESEARCH PROGRAM

While thermal burns represent the most common mechanism of burn injury, atypical burns such as frostbite, high-voltage electrical, chemical, directed energy, radiation, and nuclear represent an additional formidable threat to the health and well-being of Service Members.

Scan me to access even more information about the program.

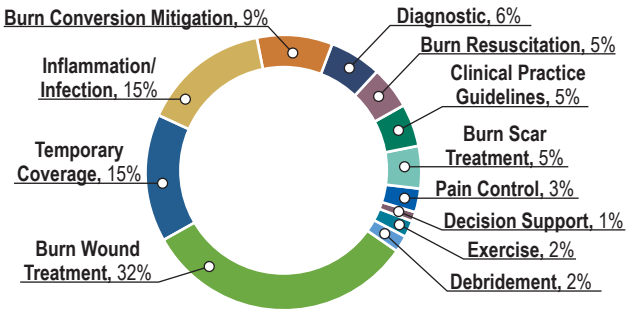
VISION *Deliver the best burn trauma care to improve health and performance outcomes in support of the Warfighter*

MISSION *Identify and address gaps in burn trauma care through military focused research*

PROGRAM HISTORY

Burn injuries sustained by military Service Members while in the line of duty, whether on the battlefield or in a military training environment, represent a continuous health burden on both the injured Service Member and the DOD health care systems in which they receive care. Historically, burn injuries afflicted some 5% to 20% of casualties during post-World War II conflicts.[1] In recent years, burns sustained during Operation Iraqi Freedom/Operation Enduring Freedom affected nearly 9% of combat-related casualties.[2] Burn injuries sustained in a combat environment are devastating and difficult to treat. This is due to severe injuries often accompanying burns such as head injury, hemorrhage, or severe orthopedic trauma. In addition, burns sustained in a deployed environment more often lead to severe burns than those sustained in the civilian setting. The majority of combat burns in recent conflicts resulted from explosive device detonation, leading to a greater Injury Severity Score, an increase in inhalation injuries, and a larger, full-thickness burn size.[3]

The Military Burn Research Program (MBRP) was initiated in 2011 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, $100M has been appropriated to the program by Congress. Through FY21, MBRP has funded 65 research projects that have provided key research insights in advancing therapies for burn-injured patients and impacted standard practice.



MBRP Portfolio by Focus Area FY11-FY21

[1] Kauvar DS, Wade CE, and Baer DG. 2009. Burn hazards of the deployed environment in wartime: Epidemiology of noncombat burns from ongoing United States military operations. *Journal of the American College of Surgeons* 209(4):453e460.

[2] Escolas SM, Archuleta DJ, Orman JA, et al. 2017. Postdischarge cause-of-death analysis of combat-related burn patients. *J Burn Care Res* Jan, 38(1):e158-e164.

[3] Kauver DS, Cancio LC, Wolf SE, et al. 2006. Comparison of combat and non-combat burns from ongoing U.S. military operations. *The Journal of Surgical Research* 132:195-200.

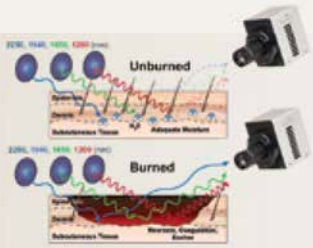
2021 Congressional Appropriations, Research Investment, and Withholds and Management Costs

Congressional Appropriations	*Research Investment*	*Withholds and Management Costs*
$10M	Clinical Translational Research Award ..... $4,328,124 Idea Development Award ..... $4,973,592 Modification to ongoing awards $189,593	USAMRDC ..... $200,000 Mgt Costs (3.31%) $324,709
Total: $10M	**Total:** $9,491,310	**Total:** $524,709

SHORT WAVE ASSESSMENT TOOL (SWAT)

Portable Burn Wound Assessment Device

- *A portable handheld, camera-based system that helps to objectively assess burn wound depth and predict healing outcomes*
- *Guides more precise treatment and debridement*



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4F ENTERORESUS

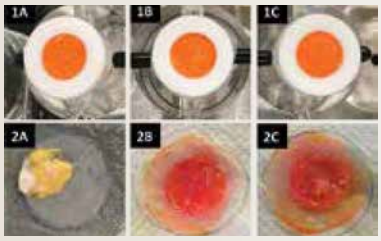
Augmenting Intravenous Fluid Resuscitation for Burn Casualties

- *Enteral resuscitation with World Health Organization oral rehydration salts and clean water via drinking and/or a nasogastric tube*
- *Operationally advantageous intervention to restore blood volume and prevent hypovolemic shock*

I-DEBRIDE™

Field-Capable Non-Surgical Debridement

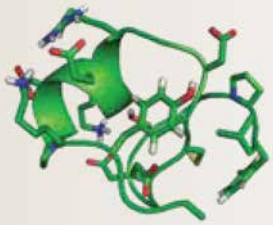
- *Based on ImmobiZyme™ technology, which combines enzymes with support matrix materials and a crosslinker to improve enzyme performance*
- *Field-capable and shelf-stable alternative to surgical removal of nonviable, damaged tissue (debridement)*



TP508

Burn Conversion Prevention Product

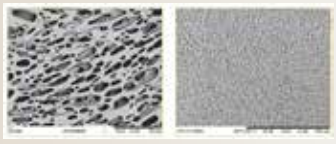
- *A thrombin-derived peptide (in topical or injection formulation) used to accelerate wound healing and wound closure after burn and lethal radiation exposure*
- *Field-accessible product may prevent the progression/conversion of burns from deep partial- to full-thickness burns*



SUPRATHEL©

Portable Synthetic Wound-Healing Skin Substitute Designed for Prolonged Field care

- *A portable synthetic wound-healing skin substitute that can be applied by nonmedical personnel*
- *May reduce the need for skin grafting, offer improved pain control, and reduce the risk of infections*



KERECIS ACELLULAR FISH SKIN GRAFTS

Development of Unique Temporizing Cover for Burn Wounds

- *Large premeshed acellular fish skin grafts for temporary wound coverage that remain shelf stable at room temperatures*
- *Field-ready product that can promote expedited skin healing in acute burns and support prolonged field care situations*

Dr. Peter Yen, Burn and Reconstructive Centers of America, Programmatic Panel Member FY21-FY22

"It is an honor and a privilege to serve CDMRP as a panelist to support the mission in advancing military burn care research. During the process, I quickly recognized how diverse the panelists are strategically, by leveraging different subject experts to create a high-impact body of work. I see CDMRP providing a vital step in bridging burn care gaps in the battlefield to protect our men and women in uniform, while many research projects will undeniably benefit the civilians of this country and the world."

MULTIPLE SCLEROSIS RESEARCH PROGRAM

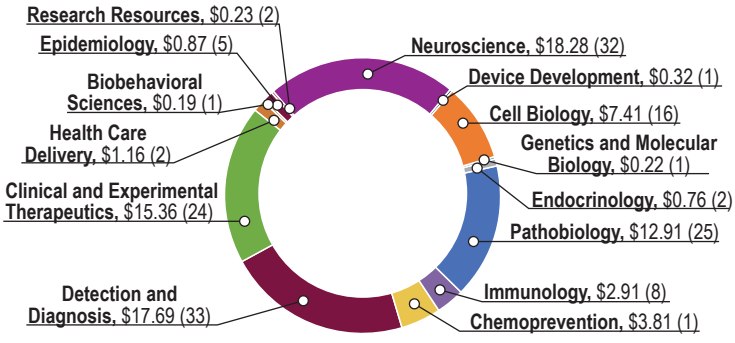
Scan me to access even more information about the program.

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

The Peer Reviewed Multiple Sclerosis Research Program (MSRP) was established in FY09, with $5M in congressional appropriations, to fund meritorious research related to multiple sclerosis (MS). It has been funded continuously since, receiving a cumulative total of $113.1M in appropriations. The overall goal of the program has been to lessen the personal and societal impact of MS 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 affects nearly 1 million individuals in the U.S. 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. Currently, there is no cure for MS.



MSRP Investment by Research Type (Number of Awards) FY09-FY21

MSRP FY22 Clinical Trial Award Focus Areas

- Promoting Repair, Neuroprotection, and Remyelination in MS
- Treatment of MS Symptoms

MSRP FY22 Early Investigator Award, Exploration-Hypothesis Development Award, and Investigator-Initiated Research Award Focus Areas

- Central Nervous System Regenerative Potential in Demyelinating Conditions
- Correlates of Disease Activity and Progression in MS
- Biology and Measurement of MS Symptoms
- Factors Contributing to or Associated with MS Etiology, Prodrome, Onset, and Disease Course

2021 Congressional Appropriations, Research Investment, and Withholds and Management Costs

Congressional Appropriations	*Research Investment*	*Withholds and Management Costs*
$20M	Clinical Trial Award – Funding Level 1 ..... $3,241,284 Clinical Trial Award – Funding Level 2 ..... $3,815,480 Early Investigator Research Award ..... $1,205,373 Exploration – Hypothesis Development Award ..... $1,601,142 Investigator-Initiated Research Award $7,803,140	USAMRDC ..... $386,798 SBIR/STTR ..... $667,000 Mgt Costs (6.75%) $1,279,783
Total: $20M	**Total:** $17,666,419	**Total:** $2,333,581

RESEARCH ACCOMPLISHMENTS

The Metabolomics-Neurofilaments-Neurodegeneration Nexus in Multiple Sclerosis Progression

Dr. Murali Ramanathan, State University of New York, Buffalo

Metabolic pathway dysregulation plays a role in neurodegeneration and progression of MS. Dr. Ramanathan's project aims to evaluate changes in metabolite levels, serum neurofilament light chain (sNfL) (biomarker for neuronal damage), and neurodegeneration in relapsing-remitting MS (RRMS) and progressive MS patients. The study analyzed baseline and 5-year follow-up samples and clinical data from MS patients and healthy controls. These evaluations help to characterize the role of metabolites and metabolic pathways in the progression of neurodegeneration in MS. Several key findings have been reported in the nine publications associated with the project, which include: (1) decreases in high-density cholesterol (HDL-C) and its related apolipoproteins are associated with increases in gray matter atrophy; (2) sNfLs increased with increasing gray matter atrophy and associated with decreased perfusion or blood flow to the thalamic region of the brain; (3) increased levels of HDL-C and its apolipoproteins were associated with increased brain perfusion. These findings indicate that lipids may have a protective effect in MS and may act as mediators of brain perfusion.

An Integrative Measurement of Common Multiple Sclerosis Symptoms Using Passive Sensing Technologies

Dr. Mayank Goel, Carnegie Mellon University

In addition to neurological symptoms, MS patients experience a variety of comorbidities such as fatigue, depression, stress, sleep disturbances, and gait imbalance. Currently, there is a lack of tracking these comorbidities in the patients' daily lives. Dr. Goel aims to use smart phones and fitness trackers to collect data such as motion, location, environment, activity, diet, and sleep. The data are used to develop and test a machine learning approach to predict depression, fatigue, and sleep disturbances, with the overall goal of predicting the onset and severity of the comorbid conditions. In addition, the investigator also assesses the effect of the "stay at home" mandate associated with containment efforts for the COVID-19 pandemic in a subset of MS patients enrolled in the study. To date, the machine learning approach has been developed and evaluated. The results demonstrated the capability of this non-invasive method to accurately detect depression, functional disability, fatigue, and sleep quality. Moving forward, the project will focus on improving performance and assessing feasibility of this integrative measurement of MS symptoms.

Study of Immune-Based Biomarkers Using the Comprehensive Longitudinal Investigation in MS at Brigham and Women's Hospital (CLIMB) Dataset

Dr. Tanuja Chitnis, Brigham and Women's Hospital

Dr. Chitnis' research is focused on finding reliable biomarkers for patients with MS who are at risk of relapse for worsening MS symptoms. Dr. Chitnis and her team compared sNfL, a protein that indicates neuro-axonal damage, from patients in remission versus those who had a newly detected lesion using MRI with gadolinium-enhancing metal contrast (Gd MRI). The team also studied the correlation between sNfL and age in patients in remission immediately after a clinical relapse and immediately after a lesion. Their findings showed sNfL as a marker of clinical relapses and Gd MRI lesions. They also observed a different correlation of sNfL levels with age depending on the Gd lesion status in MS patients. Results from this project assisted the development of a blood test for prediction of disease activity in RRMS patients. In April 2022, Quanterix received a Breakthrough Device designation from the FDA for the in-office test, which has the potential to prevent long-term disability through closer monitoring.

Physical Telerehabilitation in Patients with Multiple Sclerosis and Significant Mobility Impairment

Dr. Joel Stein, Columbia University Medical Center

The ability to travel to and participate in rehabilitation programs is a barrier for patients with MS; however, telemedicine offers a new avenue to improve access for MS patients. Drs. Joseph Finkelstein and Joel Stein at Columbia University Medical Center sought to assess the effects of a physical telerehabilitation program on functional outcomes with MS patients with mobility impairment. This clinical trial showed that patients with MS experienced improvements in fatigue, balance, muscle resistance, and their perceptions of the physical and psychological impact of MS. Moreover, physical telerehabilitation significantly improved parameters of quality of life, including physical health, pain, health perceptions, social function, cognitive function, and health distress. These findings and the overall high acceptance rate indicate that a physical telerehabilitation program is an effective way for MS patients with limited mobility to improve their quality of life, and could potentially impact other neurodegenerative diseases. Drs. Finkelstein and Stein plan to conduct a phase 3 randomized clinical trial, which will include a larger group of patients with MS, representing a broader range of disability.

NEUROFIBROMATOSIS RESEARCH PROGRAM

VISION *Decrease the clinical impact of neurofibromatosis*

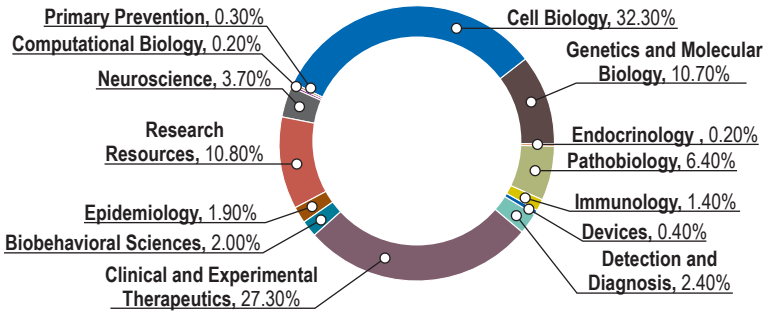
MISSION *Promote research directed toward the understanding, diagnosis, and treatment of NF1, NF2, and schwannomatosis to enhance the quality of life for persons with these disorders that impact Service Members, Veterans, and the general public*

PROGRAM HISTORY

The Neurofibromatosis Research Program (NFRP) was established in FY96 when the efforts of neurofibromatosis (NF) advocates led to a congressional appropriation of $8M. From inception until FY21, the NFRP has received $382.85M for the research of NF1, NF2, and schwannomatosis. The program obtained a funding increase in FY21 with an appropriation of $20M, and this was sustained in FY22. The program 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 471 awards spanning basic, clinical, and population-based research.

MILITARY RELEVANCE

The underlying causes of NF have a direct relationship to tumor formation in many non-cancer sarcomas and malignant cancers requiring extensive treatment and inpatient services. From 2009-2018, 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] NFRP-supported research is paving the way to finding treatments for individuals with NF that impact military Service Members, Veterans, and their beneficiaries.



NFRP Investment by Research Type FY96-FY21

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

NFRP RESEARCH RESOURCES INDEX

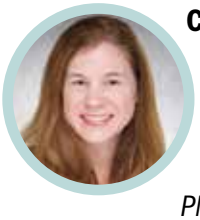
This resource exists to promote and accelerate NF research by providing resources developed by the program for information and in order to enable further collaboration among investigators. More information is available on *https://cdmrp.health.mil/nfrp/resources/nfrpresources*

Scan me to access even more information about the program.

2021 Congressional Appropriations, Research Investment, and Withholds and Management Costs

Congressional Appropriations	*Research Investment*	*Withholds and Management Costs*
$20M	Clinical Trial Award ..... $3,691,381 Clinical Trial Consortium Award ..... $5,000,000 Early Investigator Research Award ..... $328,000 Exploration – Hypothesis Development Award ..... $752,103 Investigator – Initiated Research Award ..... $3,740,827 New Investigator Award – Early Stage Investigator ..... $2,050,477 Synergistic Idea Award $2,779,975	USAMRDC ..... $400,000 Mgt Costs (6.41%)..... $1,257,237
Total: $20M	**Total:** $18,342,763	**Total:** $1,657,237

RESEARCH HIGHLIGHTS

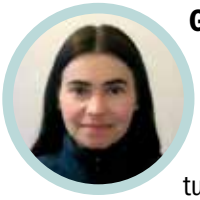


Combined CRISPR/Cas9 and Cre/LoxP approaches identify mast cells as key drivers of MPNST growth and anti-tumor immunity

Dr. Rebecca Dodd, Department of Internal Medicine, University of Iowa

PMID: 32456131

Malignant peripheral nerve sheath tumors (MPNSTs) are aggressive tumors that are often associated with neurofibromatosis type 1, (NF1). Mast cells, a type of immune cell that mediates a body's inflammatory response, are abundant in the microenvironment of MPNSTs and may alter the tumor immune landscape, thus representing a possible, critical target for improved MPNST therapy outcomes. With an FY17 New Investigator Award and another FY20 Investigator-Initiated Research Award, Dr. Rebecca Dodd's team reported an increase of mast cells in Nf1+/- mouse models of MPNST, in addition to patient samples of NF1-associated MPNSTs. Researchers exploited tumorigenesis and tumor microenvironment (i.e., CRISPR/Cas9 with Cre/loxP) genetic approaches to study the role of mast cells in MPNST progression. Using a variety and combination of other approaches, their findings discovered that constitutive depletion of mast cells delays initiation of MPNSTs and results in decreased levels of regulatory T cells that reside in the tumor while increasing levels of CD+8 T cells. Mast cell depletion also modifies tumor-associated macrophage populations. The team identified an increase in cell types that suppress the immune systems and cytokines associated with the presence of mast cells in MPNSTs as well. Furthermore, in vivo tumor intervention studies show that elimination of mast cells in established MPNSTs is sufficient to reduce tumor growth. Taken together, this data supports a role for mast cells in MPNST progression and immunosuppression, suggesting that mast cells or their cytokines may be actionable therapeutic targets.



Genetic risk factors of schwannoma tumors

Dr. Miriam Smith, University of Manchester

PMID: 33879870

Approximately 1 in 500 people will develop a schwannoma, a tumor growth in the nervous system. Schwannomatosis, a rare neurogenetic disorder, causes the development of multiple schwannomas. Genetic testing is available, but not all genetic mutations linked to schwannomatosis are known, and misdiagnosis as NF1 or NF2 has happened. Dr. Miriam Smith was awarded an FY18 NFRP Investigator-Initiated Research Award to identify missing heritable elements in a cohort of families with neurofibromatosis or schwannomatosis. The team reported no occurrences of schwannomatosis in over 1,500 patients with 22q11.2 deletion syndrome, which includes deletion of the whole LZTR1 gene (a known schwannomatosis gene) in the majority of patients. Additionally, of 110 patients with a sporadic inner ear schwannoma, only one had a whole-gene deletion of LZTR1. Results suggest that individuals with a large 22q11.2 deletion may have a reduced risk of developing a schwannoma compared to the general population. The team hopes to progress toward improving screening and therapeutic options for neurofibromatosis and schwannomatosis patients.

Dr. Sanjay Bidichandani, University of Oklahoma College of Medicine, Programmatic Panel Member FY16-FY22

"All panel members, leaders in neurofibromatosis and schwannomatosis research and advocacy, take the mission of NFRP very seriously. Our commitment to reducing the burden for families affected with these conditions is paramount. We were fortunate to see an expansion in the congressionally approved budget of the NFRP, which allowed us to allocate much needed funds towards development of potential therapies for neurofibromatosis and schwannomatosis."

Kim Bischoff, Neurofibromatosis Network, Programmatic Panel Member FY11-FY22

"I'm Kim Bischoff, the Executive Director of the national Neurofibromatosis Network, but most importantly Mom to Jennifer, my daughter with NF1. Neurofibromatosis is so fortunate to have the NFRP community of brilliant and dedicated scientists, researchers, and clinicians working together to find treatments for my daughter and for everyone affected by neurofibromatosis. I have had an amazing experience as an NFRP reviewer. As a non-scientist, at first you feel intimidated, but you soon learn how much your position as a consumer is appreciated. The sharpest minds have been attracted to NF research. New therapies are under development, with more on the horizon. We are headed in the right direction. The NFRP program is truly what gives us hope for the future."

ORTHOTICS AND PROSTHETICS OUTCOMES RESEARCH PROGRAM

Scan me to access even more information about the program.

VISION

The highest possible quality of life for Service Members, Veterans, and beneficiaries through the advancement of knowledge in orthotics- and prosthetics-related research

MISSION

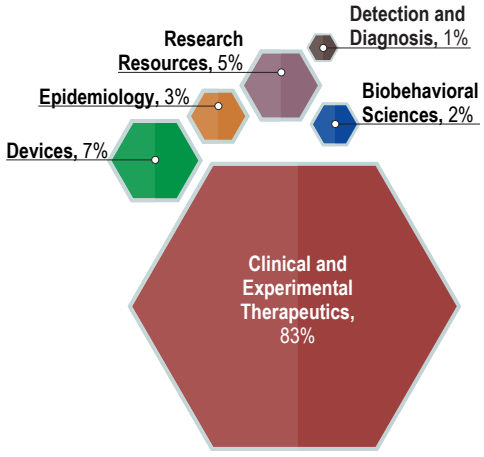
Advance orthotic and prosthetic research to optimize evidence-based care and clinical outcomes for military-relevant limb loss and limb impartment

PROGRAM HISTORY

Since its inception in FY14 through FY22, appropriations totaling $110M have been directed to the Orthotics and Prosthetics Outcomes Research Program (OPORP) to support research of exceptional scientific merit with the potential to make a significant impact on improving the health and well-being of orthotic and prosthetic users, particularly 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 orthotic and prosthetic devices, as well as improving quality of life and the ability to carry out daily activities, enhancing work productivity, and increasing return-to-work/-duty rates.

INVESTMENT STRATEGY

The OPORP supports research on outcomes-based best practices through the analysis of prosthetic and/or orthotic device options that are currently available, and not on the development of new technology or the improvement of an existing technology. Outcomes-focused research supported by the program is intended for the purpose of informing patients, clinicians, caregivers, and policymakers by advancing orthotic and prosthetic device prescription, treatment, rehabilitation, and prevention of secondary health effects.



OPORP Investments FY14-FY21 ($81,493,537 in 80 Awards)

2021 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 ..... $3,389,158 Clinical Trial Award – Funding Level 1, Funding Level 2.....$10,163,548 Orthotics and Prosthetics Outcomes Research Award – Funding Level 2 – Clinical Trial $1,500	USAMRDC ..... $289,980 SBIR/STTR ..... $501,000 Mgt Costs (4.61%) $654,814
Total: $15M	**Total:** $13,554,206	**Total:** $1,445,794

RECENTLY FUNDED HIGH-IMPACT CLINICAL RESEARCH:

Principal Investigator: *Dr. Todd Farrell, Liberating Technologies, Inc.*

Evaluation of Functional Performance of Persons with Limb Difference to Optimize Pattern Recognition Control of Power Upper Limb Prostheses

Principal Investigator: *Dr. Stefania Fatone, University of Washington*

Evaluation of Northwestern University Subischial Socket for Persons with Transfermoral Amputation and Lower Mobility Levels

Principal Investigator: *Dr. Jason Wilken, University of Iowa*

From Opinion to Evidence: Multisite Evaluation of Custom Dynamic Orthosis Best Practices

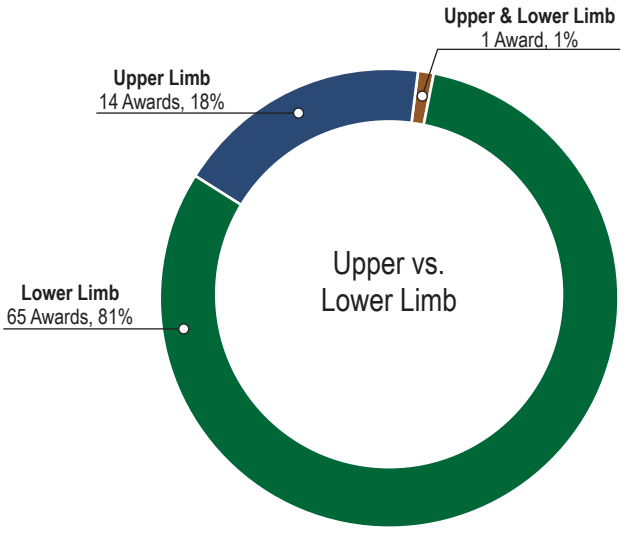
Principal Investigator: *Dr. Arun Jayaraman, Shirley Ryan AbilityLab*

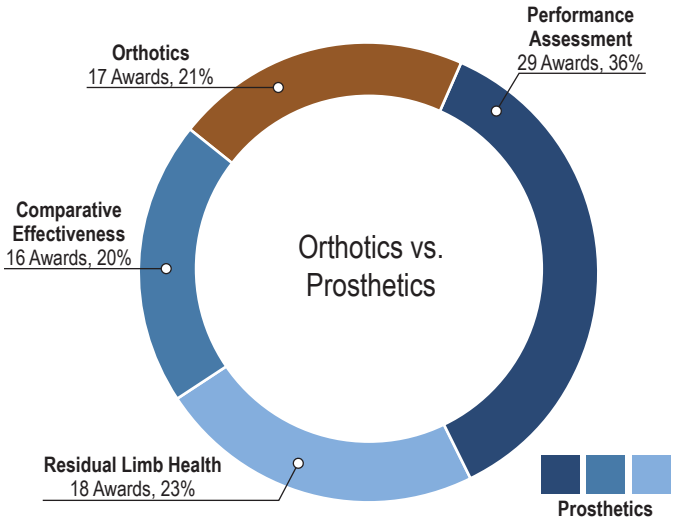
Power Forward Study: A Cross-Sector, Multisite Clinical Trial of a Power Knee-Ankle Foot Orthosis

Principal Investigator: *Dr. Matthew Wernke, The Ohio Willow Wood Company*

Protecting Limb Health Through Optimal Socket Pressure Distribution

CLASSIFICATION OF FUNDED PROJECTS BY PROJECT PRIMARY TOPIC





OVARIAN CANCER RESEARCH PROGRAM

Scan me to access even more information about the 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*

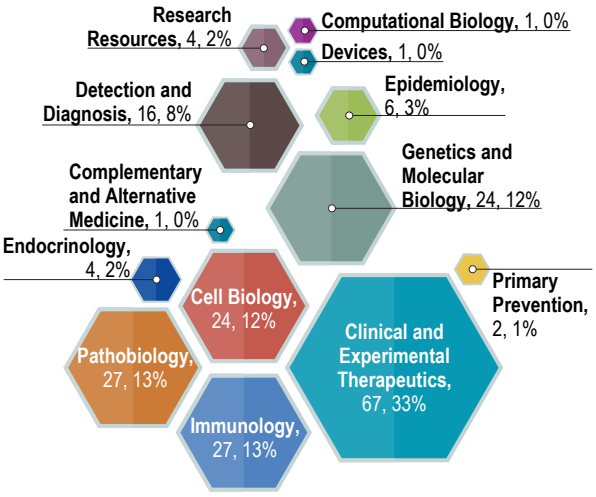
PROGRAM HISTORY

The DOD Ovarian Cancer Research Program (OCRP) was established 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-FY22, the OCRP has received $451.5M in congressional appropriations and is the second-leading funder of ovarian cancer research in the U.S. Through FY21, the OCRP has funded 648 research awards, resulting in over 2,084 peer-reviewed publications and 129 patent applications. The appropriation for OCRP for FY22 is $45.0M.

The OCRP invests in innovative and high-impact basic, translational, and clinical research, clinical trials, and Early Career Investigators in the Ovarian Cancer Academy in order to respond to the priorities of the patient and advocate community.

PROGRAM PORTFOLIO

The OCRP has transformed the landscape of ovarian cancer to the benefit of patients worldwide that can advance our understanding of biology, new discoveries, translational research, training, and sustaining the next generation of ovarian cancer scientists, and building a research infrastructure and network. OCRP invests in etiology, prevention, detection, diagnosis, survivorship, and quality of life issues and therapeutics.



OCRP Portfolio Investment by Research Type FY16-FY21

2021 Congressional Appropriations, Research Investment, and Withholds and Management Costs

Congressional Appropriations	*Research Investment*	*Withholds and Management Costs*
$35M	Clinical Translational Research Award ..... $1,382,600 Investigator-Initiated Research Award ..... $14,076,953 Omics Consortium Award..... $2,842,750 Ovarian Cancer Academy – Early-Career Investigator Award..... $1,727,760 Pilot Award ..... $6,482,615 Proteogenomics Research Award..... $399,385 Teal Expansion Award ..... $4,446,514 Modification to ongoing awards $25,027	USAMRDC ..... $675,827 SBIR/STTR ..... $1,167,000 Mgt Costs (5.35%)..... $1,773,570
Total: $35M	**Total:** $31,383,604	**Total:** $3,616,397

Cytomegalovirus Reactivation in Ovarian Cancer

Dr. Heather Nelson, University of Minnesota, Twin Cities

Dr. Nelson received a Pilot Award and her team developed an innovative digital polymerase chain reaction method to assess active cytomegalovirus (CMV) infection, which will allow them to monitor infection as patients progress through chemotherapy. Their research demonstrates that approximately half of ovarian cancer patients are experiencing CMV reactivation at the time of diagnosis, and nearly all women have active infection at some point during their chemotherapy.

Detection and Treatment of Ovarian Cancer by Targeting Tumor Extracellular Hydroxyapatite: A New Paradigm

Dr. Mohammed Tantawy, Vanderbilt University Medical Center

Dr. Tantawy received this pilot award, which helped him and his team to develop an 18F-NaF PET imaging system that can detect the deposition of extracellular hydroxyapatite from tumors as an effective alternative tool for detecting ovarian tumors. This new technique is also being evaluated in treatment tracking and can be used in the clinical monitoring of tumor burden before and after surgical debulking.

PREDICT: The Prospective Early Detection Consortium for Ovarian Cancer

Dr. Rudolf Kaaks, Deutsches Krebsforschungszentrum

Dr. Kaaks received this Omics Consortium award, which helps evaluation of tumor-associated antigens as biomarkers for earlier detection of ovarian cancer. Thirteen biomarkers had AUC ≥ 0.70 in the 9 months prior to diagnosis, suggesting potentially useful discrimination between women with or without ovarian cancer. CA125 and HE4 were among the best performing markers, together with six other proteins (FR-alpha, KLK11, ITGAV, MDK, PVRL4, and CXCL13).

PROGRAM PRIORITIES

- Understand the basic biology and etiology of ovarian cancer initiation, progression, metastasis, recurrence, genetics, and other critical events
- Develop novel therapeutic strategies for treatment and prevention
- Identify and develop new strategies for screening, early-stage detection, prevention, accurate diagnosis, and prognosis
- Identify and implement strategies to improve the survivorship and quality of life
- Address health disparities
- Improve precision medicine

[1] Military Demographics for 2012. Available here: http://www.militaryonesource.mil/12038/MOS/Reports/2012_Demographics_Report.pdf

[2] National Academy of Medicine, Ovarian Cancers: Evolving Paradigms in Research and Care, Mar. 16, 2018. Accessed Jun. 8, 2022: http://nationalacademies.org/HMD/reports/2016/state-of-ovarian-cancer

Mary Beth Mudrick, Foundation for Women's Cancer, Consumer Peer Reviewer FY18-FY20, FY22

"The front-line treatments that saved my life were clinical trials when a friend was diagnosed with ovarian cancer 28 years ago. It is a privilege and an honor to serve and support the ranks of scientists who are tirelessly searching for treatments that will better all who suffer from ovarian cancer. I do so in remembrance of my friend who served before me and lost the battle."

RELEVANCE TO MILITARY HEALTH

Approximately **19,880** new cases of ovarian cancer are estimated in the the U.S. for 2022, and an estimated **12,810** are expected to die from the disease in 2022.[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]

The OCRP Programmatic Panel includes members of the DOD Center of Excellence for Gynecologic Oncology, as well as Veterans and military retirees. These military members serve on the panel alongside ovarian cancer survivors, scientists, and clinicians. Together, they provide a unique perspective that reflects the concerns of ovarian cancer advocates, their families, the clinicians who treat them, and the relevance of this research to military health.

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

For FY20, the U.S. Congress established the Peer Reviewed Pancreatic Cancer Research Program (PCARP) with a DOD appropriation of $6M. For FY21, PCARP appropriation was $15M. In this program, PCARP will continue to 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 FY21 cycle, 15 projects were funded that address at least one of the FY21 PCARP Focus Areas.

The PCARP has 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.

PCARP FOCUS AREAS

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

- Early detection research for pancreatic cancer, including the prevalence in individuals with pre-diabetes and diabetes and/or those in underserved ethnic and minority communities
- Supportive care interventions, 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

Based on 2021 SEER data, more than 60,000 new cases of pancreatic cancer were diagnosed in the U.S., and it is the third leading cause of cancer deaths in the country.

More than 26,500 active-duty, former Service Members, and their beneficiaries were diagnosed with pancreatic cancer within the MHS from 2010-2019.

Scan me to access even more information about the program.

2021 Congressional Appropriations, Research Investment, and Withholds and Management Costs

Congressional Appropriations	*Research Investment*	*Withholds and Management Costs*
$15M	Idea Development Award ..... $11,121,781 Translational Research Partnership Award $2,487,423	USAMRDC ..... $289,980 SBIR/STTR ..... $501,000 Mgt Costs (4.22%) $599,816
Total: $15M	**Total:** $13,609,204	**Total:** $1,390,796

PARTNERING ESTABLISHED AND EARLY-CAREER INVESTIGATORS

As part of the Strategic Plan, the PCARP is invested in recruiting and retaining young investigators as they pursue careers in pancreatic cancer research. The FY22 Idea Development Award (IDA) mechanism proposes to partner an experienced PI with an Early-Career Investigator (ECI) wishing to pursue a career in pancreatic cancer research. The experienced PI on the IDA must mentor and collaborate with the ECI (Partnering PI) to promote their career development in pancreatic cancer research. The PCARP has funded nine IDA awards with a partnering PI between FY20 and FY21.

David Dessert, Facing Our Risk of Cancer Empowered, Inc., Consumer Peer Reviewer FY21-FY22

"I'm convinced that PCARP-funded research and researchers will play a key role in improving cancer outcomes. There's still so much we don't understand about cancer, and PCARP's emphasis on high-risk/high-reward projects is how we'll get the breakthroughs patients and families need."

FY21 Idea Development Award – Partnering PI Option Research Highlights

Focus Area: Understanding the relationship between oncogenic signaling and the tumor microenvironment that drives drug resistance and therapeutic response

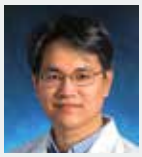

Designing Novel Strategies to Target Tumor-Promoting Functions of Pancreatic Cancer Fibroblast Subtypes

Dr. Giulia Biffi, University of Cambridge

Dr. Tobiloba Oni, Whitehead Institute for Biomedical Research

Drs. Biffi and Oni will identify novel markers, targets, and tools to profile, detect, and selectively block specific tumor-promoting roles of cancer-associated fibroblast (CAF) populations in pancreatic cancer. Their research will help illuminate specific CAF markers with the potential to be targets for future therapies against pancreatic cancer progression.

Focus Area: Understanding precursors, origins, and early progression of pancreatic cancer

3D Multiscale Analysis of Malignant Progression in Human Pancreatic Cancer

Dr. Laura Wood, Johns Hopkins University

Dr. Won Ho, Johns Hopkins University

The Johns Hopkins team will investigate the molecular and cellular alternations from the key transition point in pancreatic cancer tumorigenesis, namely from a curable precancerous neoplasm to an incurable invasive cancer. The investigators will determine an important proof-of-concept, looking at both tumor cells and the tumor microenvironment while employing three-dimensional analysis to elucidate the mechanisms of pancreatic cancer invasion.

Focus Area: Understanding the events that promote pancreatic cancer metastasis


Controlling the Burden of Metastatic Disease in Pancreatic Ductal Adenocarcinoma

Dr. Ben Stanger, University of Pennsylvania

Dr. John McAuliffe, Albert Einstein College of Medicine of Yeshiva University

Drs. Stanger and McAuliffe will examine how different epithelial-mesenchymal phenotypes are related to metastatic disease and how tumor microenvironment of metastasis doorways, composed of a tumor cell, a macrophage, and an endothelial cell, promote the passage of tumor cells through the bloodstream to distant sites. They will also investigate how Rebastinib, a drug that has shown potential in the prevention of metastatic spread in other cancers, could help inhibit pancreatic cancer metastasis.

Focus Area: Early detection research for pancreatic cancer, including studies of individuals with pre-diabetes and diabetes and/or those in underserved ethnic and minority communities


Risk Stratification of Pancreatic Ductal Adenocarcinoma in New-Onset Diabetes Using Artificial Intelligence Analysis of Retinal Images

Dr. Debiao Li, Cedars-Sinai Medical Center

Dr. Touseef Ahmad Qureshi, Cedars-Sinai Medical Center

The study team will investigate pancreatic ductal adenocarcinoma (PDAC)-indicative features from retinal images of patients diagnosed with new onset diabetes (NOD) using artificial intelligence analysis. The determination of NOD patients with a high risk of developing pancreatic cancer will allow regular targeted screening to help detect this cancer at an early stage. Being able to detect PDAC at this stage can help decelerate disease progression or even prevent PDAC.

PARKINSON'S RESEARCH PROGRAM

Studies have found that military deployment is associated with a 1.8-fold increased risk of PD.

The PRP challenges the scientific community to develop the most impactful research that will advance the understanding of the disease, with the ultimate goal of ending PD.

Scan me to access even more information about the program.

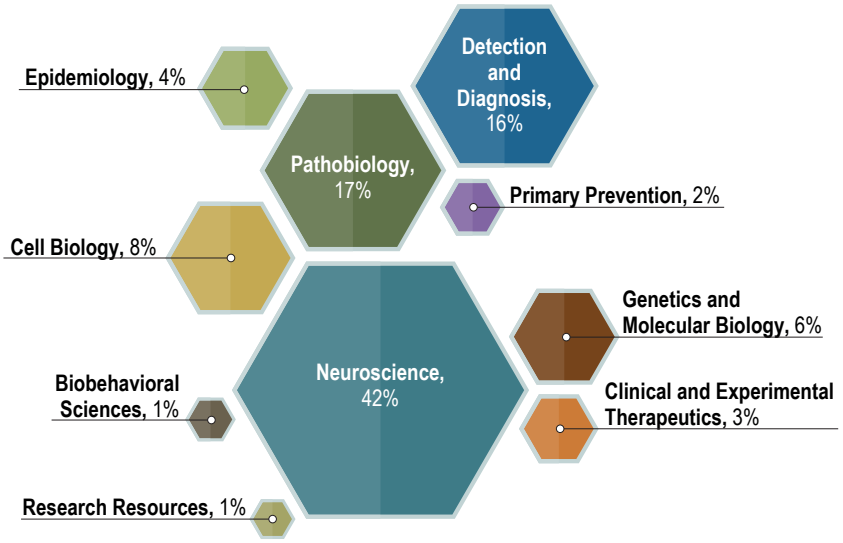
VISION *Increase the understanding of Parkinson's disease and to develop treatments towards a cure*

MISSION *Support high-impact Parkinson's research to benefit both the military and the American public*

PROGRAM HISTORY

Based on data from the Parkinson's Foundation, there are almost one million people in the U.S. living with Parkinson's Disease (PD), and each year that number is expected to increase by 60,000. With more than 10 million people living with PD worldwide, an estimated 4% of that population has been diagnosed before the age of 50.[1] Since 1997, the CDMRP has funded PD research through the Neurotoxin Exposure Treatment Parkinson's (NETP) Program. From FY97 through FY21, there has been a total of $484.75M appropriated for PD research.

For FY22, the U.S. Congress transitioned the NETP Program to the Parkinson's Research Program (PRP) with an appropriation of $16M. The transition broadened the research from neurotoxin exposure treatment PD research to all types of PD research. Program announcements to be solicited for FY22 are the Early Investigator Research Award, the Investigator-Initiated Research Award, and the Synergistic Idea Award. The PRP has been congressionally appropriated to support research of exceptional scientific merit in PD. All applications must address one of the program's Focus Areas.



NETP Portfolio Investment by Research Type FY16-FY21

[1] https://www.parkinson.org/Understanding-Parkinsons/Statistics

2021 Congressional Appropriations, Research Investment, and Withholds and Management Costs

Congressional Appropriations	*Research Investment*	*Withholds and Management Costs*
$16M	Early Investigator Research Award ..... $1,996,410 Investigator-Initiated Research Award ..... $7,945,815 Synergistic Idea Award $5,319,566	USAMRDC ..... $319,755 Mgt Costs (2.67%) $418,454
Total: $16M	**Total:** $15,261,791	**Total:** $738,209

Reducing Tau as a Therapeutic Strategy for Improving Cognitive Dysfunction in Parkinson's Disease

Dr. Laura A. Volpicelli-Daley, University of Alabama at Birmingham

One of the most burdensome effects of PD is cognitive change. Treatments for cognitive effects provide little relief for most patients and do not prevent progressive deterioration. Dr. Laura A. Volpicelli-Daley received a DOD award to examine whether the protein tau is implicated in PD, as it is in other neurological conditions.

Knowing the genes for tau and alpha-synuclein are consistently associated as risk factors for PD, she asked whether tau and alpha-synuclein interact to cause cognitive changes in PD and whether the absence of tau would prevent neuronal dysfunction and behavioral defects in cognition and mood disorders. Her hypothesis was that the tau protein causes neuronal dysfunction before development of alpha-synuclein aggregates and initiates the cognitive dysfunction seen in PD. Working with Dr. Erik Roberson, an expert in tau at the University of Alabama at Birmingham, Dr. Volpicelli-Daley used a novel mouse model with reduced or abolished tau levels. Alpha-synuclein fibrils were injected into neurons in the striatum to induce formation of alpha-synuclein inclusions in brain regions important for cognitive function.

Findings from Dr. Volpicelli-Daley's study and additional published research suggest that reducing tau prevents the formation of fibril-induced alpha-synuclein inclusions and improves behavioral tests of cognition.

"I received a Career Progression Award from the DOD in 2015 that helped launch my career as a tenure-track assistant professor at the University of Alabama Birmingham. NIH funding and R01 grants are difficult to obtain for an early-career researcher without prior awards that substantiate their contributions to science."

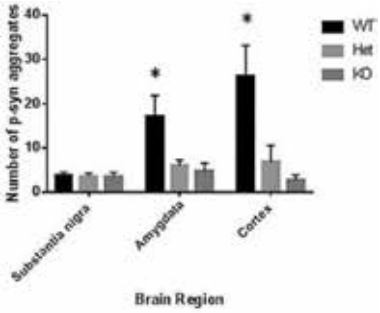
Parkinson's Disease Interventions Points Identified in Exercise Studies

Dr. Michael Salvatore, University of North Texas Health Science Center

Dr. Michael Salvatore, received an award from the CDMRP's NETP program to investigate the neurobiological mechanisms of exercise in two animal models of PD. His study, "Increasing Nigral Tyrosine Hydroxylase Expression as a Mechanism of Exercise-Mediated Recovery: Evaluation in Toxin and Rat Parkinson's Disease Genetic Models," was awarded in FY18.

The project will determine molecular pathways affected by exercise and specific intervention points in the molecular pathways to develop new treatments for PD. More specifically, Dr. Salvatore and his colleagues, Dr. Christopher Bishop at Binghamton University and Dr. Jason Richardson at Florida International University, are looking at the expression of the glutamate transporter GLAST and the GDNF family receptor GFR alpha1 mechanisms as regulators of tyrosine hydroxylase (TH) expression in the Substantia nigra following exercise. They are investigating whether these molecules act as regulators to mediate recovery of motor function related to exercise in PD.

Outcomes to date suggest parkinsonian signs are associated with the somatodendritic region of the Substantial nigra and that augmenting dopamine signaling improves signs of Parkinsonism even after initial loss of dopaminergic neurons. Their findings suggest that tyrosine hydroxylase loss in the Substantia nigra is progressive in the lesion timeline and is progressive in both hemispheres, whereas striatal TH loss reaches a peak early in the condition. Further studies by the investigators will help determine whether exercise restores striatal TH loss.



Reducing tau inhibits the formation of seeded α-synuclein formation in the amygdala and cortex

Kelly Sweeney, Parkinson's Resources of Oregon, Programmatic Panel Member FY17-FY22

"Speaking for Consumers, i.e., PD Patients, there is not a comparable program that I am exposed to that opens funding for creative, disruptive, and challenging science. I am grateful for the funding the CDMRP offers. It's a difference maker."

Dr. Daniel Weintraub, University of Pennsylvania, Programmatic Panel Member FY19-FY22

"As a psychiatrist, I enjoy being on the review panel for the Parkinson's program, as it's one of the few research programs for Parkinson's disease that has a specific focus on the common and problematic non-motor features of Parkinson's, including psychiatric symptoms and cognitive complications. This is crucial to improving the lives of people living with Parkinson's disease."

PEER REVIEWED ALZHEIMER'S RESEARCH PROGRAM

Scan me to access even more information about the program.

VISION

To address and mitigate long-term implications of traumatic brain injury and military service as they pertain to Alzheimer's disease and Alzheimer's disease-related dementias

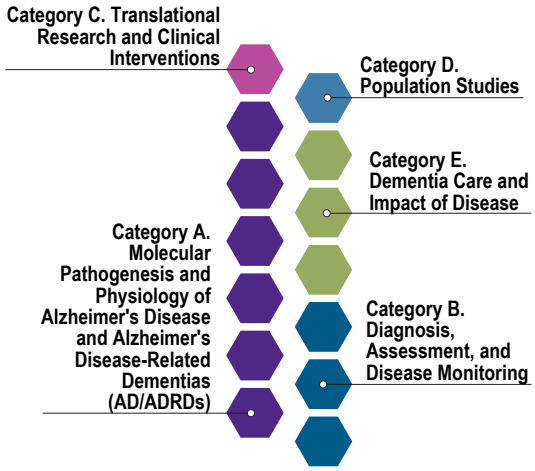
MISSION

Support research to (1) understand the association between TBI and other military service-related risk factors and Alzheimer's disease/Alzheimer's disease-related dementias, and (2) improve quality of life and reduce the burden on affected individuals and caregivers for the military, Veterans, and the public

PROGRAM HISTORY

Military personnel face an increased risk for developing Alzheimer's disease (AD) or a related dementia as they age. 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, and depression long before a diagnosis is established. Currently, there are no effective treatments for dementia.

The Peer Reviewed Alzheimer's Research Program (PRARP) was established by Congress in FY11 to support research that addresses the long-term consequences of TBIs as they pertain to AD and AD-related dementias (ADRD). Since the PRARP's inception in FY11 through FY21, congressional appropriations totaling $153M have been allocated toward research that will provide meaningful outcomes to support caregivers and persons with AD and ADRD. Thus far, the PRARP has funded 152 awards, emphasizing not only basic research related to understanding and diagnosing the molecular basis of AD/ADRD after military service, but also tools and strategies that can be used to improve the quality of life of individuals living with AD or ADRD. The FY22 PRARP congressional appropriation is $15M.



PRARP Classification by Common Alzheimer's Disease Research Ontology FY16-FY21

2021 Congressional Appropriations, Research Investment, and Withholds and Management Costs

Congressional Appropriations	*Research Investment*		*Withholds and Management Costs*	
$15M	Accelerating Diagnostics Research Award	$5,578,750	USAMRDC	$278,604
	Convergence Science Research Award	$5,788,862	SBIR/STTR	$501,000
	Innovations in Care and Support Award	$522,386	Mgt Costs (5.45%)	$775,606
	Research Partnership Award	$1,554,792		
Total: $15M		**Total:** $13,444,790		**Total:** $1,555,210

Dr. Linda Chao leads a FY16 PRARP Quality of Life Research Award ($700k; W81XWH-21-1-0147) utilizing the Preventing Loss of Independence through Exercise (PLIÉ) program to improve quality of life and neurological function in individuals with mild cognitive impairment or memory decline and their caregivers. The PLIÉ intervention involves mind-body interventions aimed at facilitating memory, body mindfulness, and social connection. Individuals who participated in PLIÉ showed improvements in neural functional connectivity, cognition, self-regulation, well-being, and significantly reduced feelings of social isolation. This intervention is being delivered virtually via telehealth in their follow-up FY20 PRARP Leveraging Approaches for Innovation in Care and Support Award ($2.6M).

Traditional laboratory tests for cognitive decline rely on self- and caregiver-reports and clinically administered assays that are not relevant to real-life situations. Dr. Michael Barnett addresses this problem with a FY18 PRARP New Investigator Research Award ($300k; W81XWH-19-1-0798), in which they developed the Virtual Environment Grocery Store (VEGS) as a new assay using real-life scenarios (e.g., shopping from list, budgeting, etc.) to diagnose cognitive impairment. VEGS performance was able to detect impaired vs. non-impaired adults with a ~3% error rate (N=71).

Dr. Kristine Yaffe leads an epidemiological FY17 PRARP Research Partnership Award ($1.3M; W81XWH-18-1-0692) characterizing the relationship between genetics, co-morbidities, and ethnicity on cognitive decline and dementia in Veterans with a history of TBI. Leveraging huge health care datasets from the VA and the Duke Twin Registry of WWII Veterans, studies revealed that female Veterans have a higher risk of dementia post-TBI, but TBI significantly increased dementia risk across both sexes and all racial groups. Moreover, co-morbidities such as psychiatric diagnoses (PTSD, depression), cardiovascular disease, and drug abuse disorders increased dementia risk post-TBI.

Dr. Sameer Shah leads a FY18 PRARP Convergence Science Research Award ($800k; W81XWH-19-1-0315) that characterizes the link between TBI and AD/ADRD development using an innovative neuron-stretch model. Their team recently published a report demonstrating that their model mimics disease-related pathology in AD brains, suggesting this model is relevant to use for therapeutic investigation.

Dr. Jiadi Xu leads a FY17 PRARP New Investigator Research Award ($300k; W81XWH-18-1-0797) developing and leveraging an innovative MRI assay, called rNOE-CEST, to examine changes in the molecular movement of proteins in the neuropathological progression of AD/ADRD in mice and humans. The rNOE-CEST signal is associated with accumulation in an AD mouse model and developed a pipeline for analysis of this type of imaging for future studies.

FOCUS AREAS

Consistent with the PRARP's mission and vision, the program seeks to fund research focusing on the intersection of TBI-AD/ADRD, including understanding mechanisms, biomarkers, and risk factors to identify interventions that have near-term impact. The PRARP FY22 Focus Areas are:

Caregiver, Family, and Individual Support

Focuses on the need for technologies, assessments, interventions, or devices that enhance the lives of those living with AD/ADRD and providing care, especially to Service Members and Veterans.

Diagnostic, Environmental, and Prognostic Factors

Focuses on technologies, tests, questionnaires, devices, biomarkers, or analyses, including epidemiological research, to detect the relationship between military service-related risk factors and AD/ADRD.

Foundational Research

Focuses on research that examines the interrelationship between TBI, military service-related factors, and subsequent AD/ADRD.

PEER REVIEWED CANCER RESEARCH PROGRAM

Scan me to access even more information about the program.

VISION

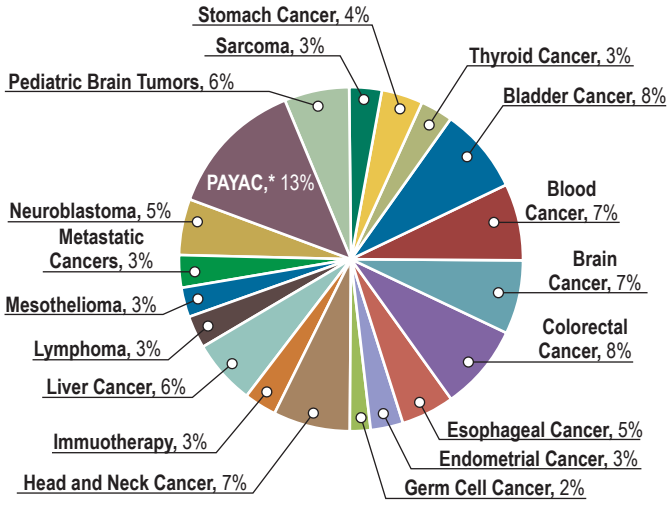
To advance mission readiness of U.S. military members affected by cancer and to improve quality of life by decreasing the burden of cancer on Service Members, their families, Veterans, and the American public

MISSION

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

PROGRAM HISTORY

As a dynamic cancer funding research program, the Peer Reviewed Cancer Research Program (PRCRP) answers the call from the U.S. Congress to invest in a variety of different cancers. These congressionally directed cancers or research areas (Topic Areas) change yearly but must be relevant to military health for Service Members and their families. The PRCRP takes the charge from Congress and funds innovative and impactful science for the benefit of Service Members, their families, Veterans, and the American public. With an ever fluid portfolio of different cancers, the PRCRP manages portfolio areas to fund the best and brightest research that ultimately impacts patient communities. Utilizing a variety of funding mechanisms from early ideas to convergent science to clinical trials, the PRCRP positions itself to address each Topic Area and advance clinical applicability in cancer research.



PRCRP Percentage of Research Dollars Invested FY20-FY21

* PAYAC - Pediatric, Adolescents, and Young Adult Cancers

2021 Congressional Appropriations, Research Investment, and Withholds and Management Costs

Congressional Appropriations	*Research Investment*		*Withholds and Management Costs*	
$115M	Behavioral Health Science Award	$4,230,272	USAMRDC	$2,223,280
	Career Development Award	$12,196,455	SBIR/STTR	$3,836,000
	Idea Award	$13,763,527	Mgt Costs (5.64%)	$6,144,549
	Impact Award	$35,008,692		
	Translational Team Science Award	$37,540,020		
Total: $115M		**Total:** $102,738,966		**Total:** $12,203,829

FUNDING THE FUTURE OF CANCER RESEARCH

Neuro-Oncology and Pediatric Oncology – Brain Cancer and Neuroblastoma

Dr. Jianmei Leavenworth, University of Alabama at Birmingham – Dr. Jianmei Leavenworth studies malignant glioma, a type of brain cancer. Her team investigated the anti-glioma responses of IL-12-oncolytic herpes simplex viral therapy and showed that PD-1+ CD4+ T cells may be therapeutic biomarkers that predict which patients with brain tumors are likely to benefit from IL12-oHSV immunotherapy.

Dr. George Hucks, and Dr. Barbara Savoldo, University of North Carolina – Utilizing the promising chimeric antigen receptor T cell therapy (CAR-T), the team at UNC plans to attack solid pediatric tumors. Though CAR-T continues to remain an elusive therapy for solid tumors, Drs. Hucks and Savoldo's approach may improve the antitumor activity of CAR-T cells through enhanced survival and efficacy methods at the tumor site. A phase 1 trial currently underway tests this new method on children with relapsed/refractory neuroblastoma.

Hematology Oncology – Blood Cancers, Myeloma, and Lymphoma

Dr. Rosa Lapalombella, Ohio State University – Dr. Lapalombella's seminal work on the overexpression of a protein called exportin (XPO1) led to the initial phase 1 study of selinexor in advanced hematological malignancies, and the FDA approval of XPOVIO© (selinexor) for the treatment of multiple myeloma and relapsed or refractory diffuse large B-cell lymphoma. Analogues of selinexor are currently being studied to improve responses and extend to other blood cancers.

Gastrointestinal Oncology – Colorectal Cancer and Liver Cancer

Dr. Scott Waldman, Thomas Jefferson University, Dr. David Weinberg, Institute for Cancer Research, and Dr. Jason Dominitz, Seattle Institute for Biomedical and Clinical Research – The team headed by Dr. Waldman studies the colorectal receptor GUCY2C and its potential to inhibit the development or spread of colorectal cancer (CRC). Their prevention strategy trial includes using oral linaclotide in patients with established adenomas or carcinomas to inhibit CRC epithelial dysfunction and hyperproliferation.

Dr. Jinjun Shi, Brigham and Women's Hospital – To reprogram the immunosuppressive tumor microenvironment of liver cancer, Dr. Shi restored the function of the p53 master regulator gene using mRNA nanoparticles in preclinical laboratory work. This demonstrated that, in combination with immune checkpoint blockade, the p53 mRNA nanoparticle technology induced suppression of tumor growth and significantly increased anti-tumor immune responses in liver cancer models.

General Oncology – Urology Bladder Cancer

Dr. Keith Chan, Cedars-Sinai Medical Center – Dr. Chan investigated improving outcomes for patients with advanced bladder cancer. Inflammatory mediators released by chemotherapy often cause immunogenic cell death (ICD). Gemcitabine, a bladder cancer treatment, initiates the inflammatory response but not ICD due to inhibition by prostaglandin E2 (PGE2). Using the PGE2 inhibitor celecoxib in combination with gemcitabine, Dr. Chan overcame the inhibition and sensitized bladder cancer cells to ICD.

PEER REVIEWED MEDICAL RESEARCH PROGRAM

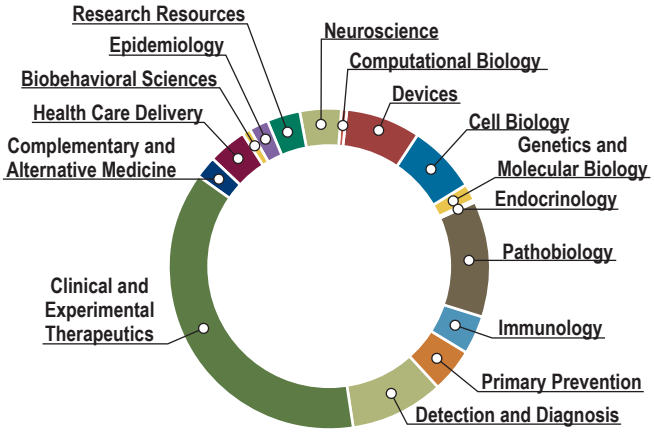
VISION *Improve the health, well-being, and care of all military Service Members, Veterans, and beneficiaries*

MISSION *Encourage, identify, select, and manage medical research projects of clear scientific merit that lead to impactful advances in military health care*

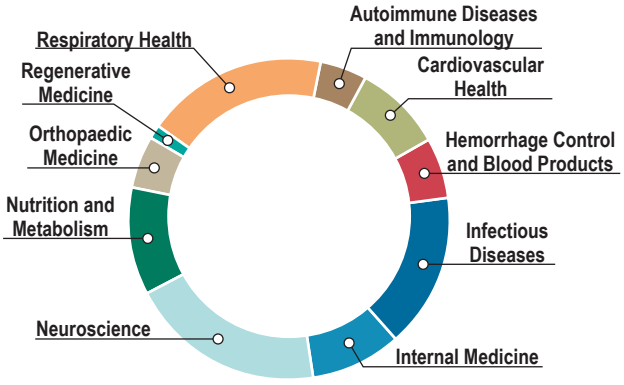
PROGRAM HISTORY

Since Congress established the Peer Reviewed Medical Research Program (PRMRP) in FY99, the program has received congressional appropriations totaling $3.45B and has supported more than 1,950 research awards in 168 unique Topic Areas representing various diseases and conditions, resulting in over 4,800 peer-reviewed publications and nearly 400 patent applications or patents granted. The FY22 congressional appropriation is $370M to solicit research applications in 50 Topic Areas.

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. PRMRP 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 (see figures below).



PRMRP Investment by Research Type FY20-FY21



PRMRP Investment by Portfolio FY20-FY21 (394 Awards Totaling $723.3M)

2021 Congressional Appropriations, Research Investment, and Withholds and Management Costs

Congressional Appropriations	*Research Investment*		*Withholds and Management Costs*	
$370M	Clinical Trial Award	$26,917,098	USAMRDC	$7,153,200
	Discovery Award	$19,816,887	SBIR/STTR	$12,340,000
	Expansion Award	$34,611,617	Mgt Costs (4.28%)	$15,005,044
	Focused Program Award	$50,107,519		
	Investigator Initiated Award	$119,133,001		
	Technology/Therapeutic Development Award	$61,657,737		
	Modification to ongoing awards	$8,932,453		
Total: $370M		**Total:** $335,955,771		**Total:** $34,498,244

PRMRP-SUPPORTED PRODUCTS

Neuroscience

Banyan Brain Trauma Indicator: A rapid, FDA-approved test utilizing blood-based biomarkers to predict the presence of brain lesions after head injury

Naxitamab (Danyelza®; HU3F8): An FDA-approved monoclonal antibody treatment for neuroblastoma in the bone or bone marrow

Respiratory Health

Clofazimine for COVID-19: An FDA-approved drug for treating leprosy – currently in a clinical trial to expand indications for COVID-19

BIO-300: An oral powder to protect lungs from radiation damage and SARS-CoV-2 infection – currently in preclinical testing

Infectious Diseases

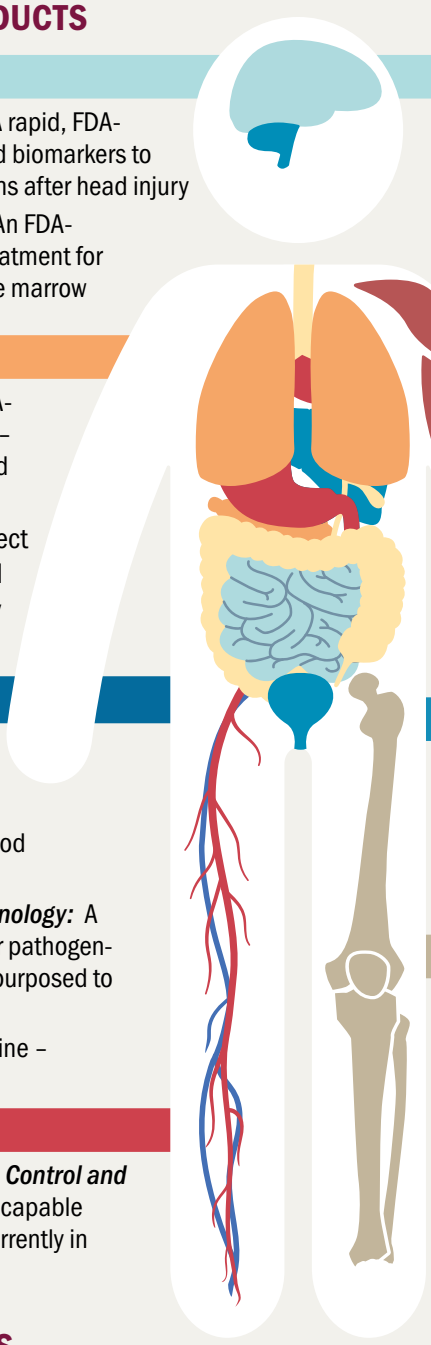
MeMED VB® AND MeMED KEY®: A rapid, FDA-approved diagnostic technology to distinguish between bacterial and viral infections in blood samples

Mirasol Pathogen Reduction Technology: A technology originally developed for pathogen-inactivation in blood now being repurposed to rapidly produce vaccines

Flugen: A universal influenza vaccine – currently in clinical trials

Hemorrhage Control

SHARC (Self-Sensing Hemorrhage Control and Resuscitative Catheter): A device capable of enabling precise blood flow – currently in preclinical testing



Neuroscience

Erenumab for Post-Traumatic Headache (PTH): An FDA-approved monoclonal antibody treatment for migraines – currently in a clinical trial to expand indications to PTH

CBTi Web: A provider-focused, web-based learning course in cognitive behavioral therapy for insomnia

Cardiovascular Health

ATAD3 Duplications: A genetic mutation for mitochondrial diseases incorporated in Victorian Clinical Genetics Services prenatal testing panel

LEAP (Low-Force Expanding-Adaptable Pediatric) Valve: A cardiac valve designed to grow with children – currently in preclinical testing

Internal Medicine

Metformin for Polycystic Kidney Disease (PKD): An FDA-approved drug for treating diabetes – currently in a clinical trial to expand indications to PKD

Orthopaedic Medicine

Osteo Adapt SP: A synthetic bone scaffold to promote bone regrowth and healing – currently in preclinical testing

SPRINT® PNS System: A device for providing non-opioid pain relief to treat chronic pain – currently in a clinical trial to expand indications to back pain

Scan me to access even more information about the program.

FY22 PRMRP TOPIC AREAS

Respiratory Health
- Pulmonary Fibrosis
- Respiratory Health
- Trauma

Autoimmune Diseases and Immunology
- Food Allergies
- Guillain-Barré Syndrome
- Inflammatory Bowel Disease
- Rheumatoid Arthritis

Cardiovascular Health
- Cardiomyopathy
- Congenital Heart Disease
- Familial Hypercholesterolemia
- Hypercholesterolemia
- Hypertension
- Vascular Malformations
- Women's Heart Disease

Hemorrhage Control and Blood Products
- Hemorrhage Control
- Pathogen-Inactivated Blood Products
- Platelet-Like Cell Production
- Trauma

Infectious Diseases
- Hepatitis B
- Malaria
- Plant-Based Vaccines
- Viral Diseases

Internal Medicine
- Ehlers-Danlos Syndrome
- Endometriosis
- Epidermolysis Bullosa
- Focal Segmental Glomerulosclerosis
- Interstitial Cystitis
- Nephrotic Syndrome
- Pancreatitis
- Polycystic Kidney Disease
- Pressure Ulcers

Neuroscience
- Dystonia
- Eating Disorders
- Fragile X
- Friedreich's Ataxia
- Frontotemporal Degeneration
- Hydrocephalus
- Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome
- Myotonic Dystrophy
- Non-Opioid Therapy for Pain Management
- Peripheral Neuropathy
- Rett Syndrome
- Sleep Disorders and Restriction
- Suicide Prevention
- Trauma

Nutrition and Metabolism
- Diabetes
- Mitochondrial Disease
- Nutrition Optimization

Orthopaedic Medicine
- Arthritis
- Fibrous Dysplasia
- Musculoskeletal Disorders (related to acute bone conditions and injuries)

Aligned with Multiple Portfolios
- Sustained Release Drug Delivery

PEER REVIEWED ORTHOPAEDIC RESEARCH PROGRAM

Scan me to access even more information about the program.

VISION

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

MISSION

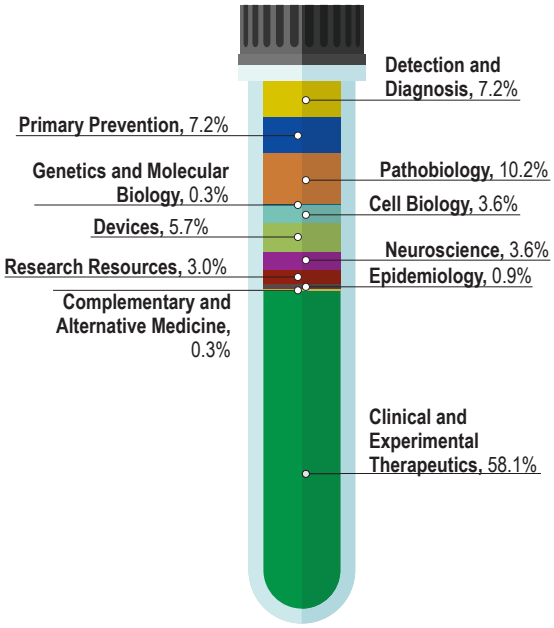
Address the most significant gaps in care for the leading burden of injury and for facilitating return-to-duty by funding innovative, high-impact, clinically relevant research to advance optimal treatment and rehabilitation from musculoskeletal injuries sustained during combat-related activities

PROGRAM HISTORY

Since its inception in 2009, the DOD Peer Reviewed Orthopaedic Research Program (PRORP) had dedicated its congressional appropriations, totaling $488.5M through FY22, to support military-relevant orthopaedic research that will also benefit the treatment and care of orthopedically injured persons in the general population. The PRORP has funded 314 orthopaedic research projects (with an additional 20 awards planned by September 30, 2022) focused on topics including treatment, surgical and rehabilitation interventions, prevention of complications, and prosthetic/orthotic devices.

INVESTMENT STRATEGY

Orthopaedic injuries have a profound impact on military readiness and return to work/activity/duty. Early stabilization, treatment, and rehabilitation of these injuries in both civilian and military populations have led to better outcomes, particularly in the prevention of secondary complications and in minimizing morbidity. The PRORP supports research that will have an impact on the lives of all individuals that have sustained a major musculoskeletal injury.



PRORP Portfolio by Research Type FY09-FY21

2021 Congressional Appropriations, Research Investment, and Withholds and Management Costs

Congressional Appropriations	*Research Investment*	*Withholds and Management Costs*
$30M	Applied Research Award ..... $ 3,621,884 Clinical Translational Research Award ..... $14,388,615 Clinical Trial Award ..... $8,992,786 Modification to ongoing awards $363,803	USAMRDC ..... $593,226 SBIR/STTR ..... $1,000,000 Mgt Costs (3.66%) $1,039,684
Total: $30M	**Total:** $27,367,088	**Total:** $2,632,910

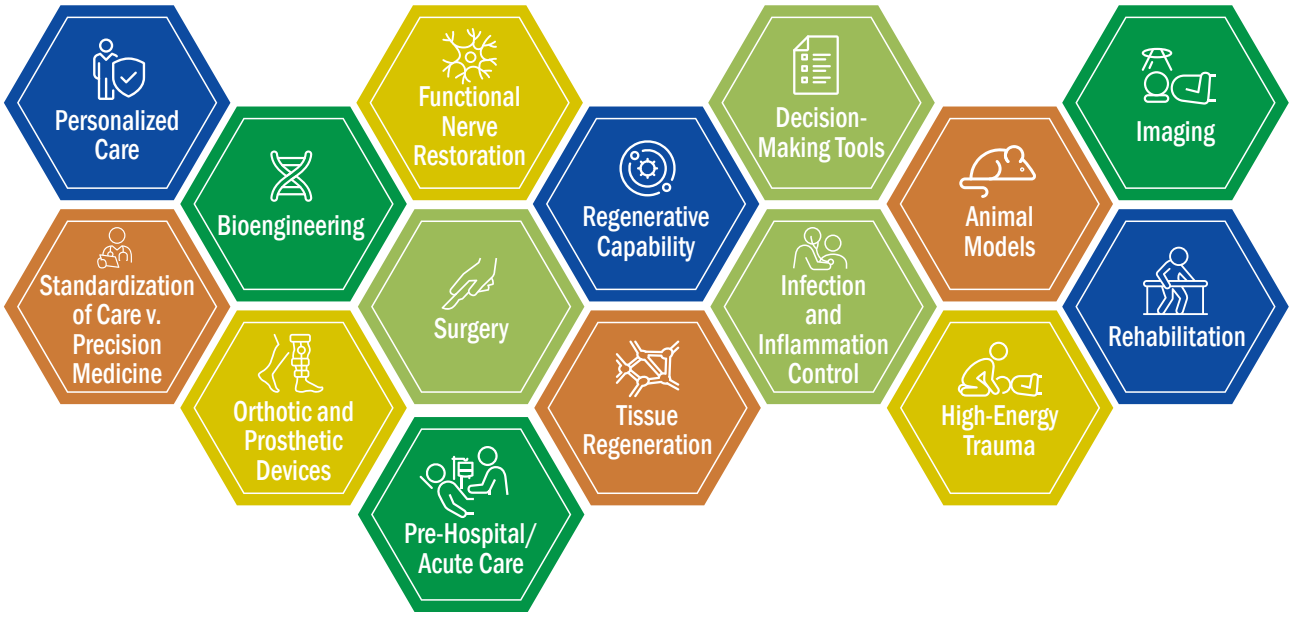
FOCUS AREAS

The orthopaedic care field has benefited from many successes; however, many challenges still exist that prevent some injured Service Members from achieving optimal recovery. 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 FY22 PRORP required all applications to address at least one of the following PRORP Focus Areas:

- **Compartment Syndrome and/or Reperfusion Injury**
  - ◊ Novel treatment strategies to improve current diagnoses for compartment syndrome and/or reperfusion injury.
- **Composite Tissue Regeneration**
  - ◊ Advanced tissue regeneration therapeutics in composite tissue for the restoration of traumatically injured extremities.
- **Limb Stabilization and Protection**
  - ◊ Development and/or clinical evaluation of rapid limb stabilization and novel wound protectants for severely or critically wounded limbs to enable prolonged care and eventual transport to the point of definitive treatment.
- **Osseointegraton**
  - ◊ Identification of best practices to address infection, rejection, and/or failure of percutaneous osseointegrated prosthetic limbs.
- **Prostheses and Orthoses**
  - ◊ Development of high-performance novel prosthetic or orthotic devices designed to enhance whole-person performance and decrease pain in patients with amputation and limb salvage and impairment.
- **Retention Strategies**
  - ◊ Development, optimization, and/or validation of battlefield-feasible diagnostic capabilities, decision support tools, interventions, and/or rehabilitation strategies that can facilitate retention on duty or avoid reinjury for common combat-related musculoskeletal injuries, addressing both *Battlefield Care* and *Return to Duty*.
- **Tissue Regeneration Therapeutics**
  - ◊ Advanced tissue regeneration therapeutics in nerve, muscle, and/or composite tissue for the restoration of traumatically injured extremities.
- **Translation of Early Findings**
  - ◊ Translation of early research findings in the orthopaedic surgical care Topic Areas of *Soft Tissue Trauma* and *Fracture-Related Infection* to move the research toward clinical trials and clinical practice.

2021 STAKEHOLDERS MEETING OUTCOMES

In September 2021, the PRORP hosted a stakeholders meeting to capture the critical knowledge and capability gaps in orthopaedic research and care. Click or scan the QR code on the previous page for access to the complete meeting summary. The most important PRORP-relevant stakeholder-identified gaps will be incorporated into the updated PRORP Strategic Plan, and are highlighted below.



PROSTATE CANCER RESEARCH PROGRAM

Prostate cancer
is a real threat to
U.S. Service Members
80% of the **active-duty population are men**

211,625
Active Service Members
and DOD beneficiaries were treated for prostate cancer in MHS between 2010–2019*
**Data provided by the Armed Forces Health Surveillance Branch based on electronic records within Defense Medical Surveillance System.*

Scan me to access even more information about the program.

VISION *Conquer prostate cancer*

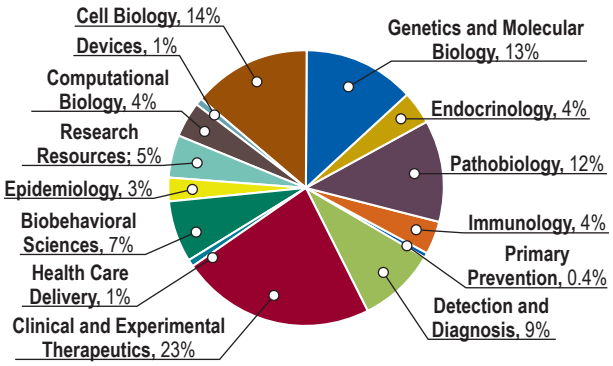
MISSION *Fund research that will lead to the elimination of death from prostate cancer and enhance the well-being of Service Members, Veterans, and all men experiencing the impact of the disease*

PROGRAM HISTORY

Since its inception in 1997, and over its 25-year history of congressional support totaling nearly $2.15B, the 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 has made unprecedented inroads in supporting the development of new treatments for advanced PCa; has been the leading supporter of research aimed at understanding and resolving health disparities in PCa incidence and mortality; has positively impacted PCa standard of care received by Service Members, Veterans, and the general public, including those treated in the MHS; 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 PCa by identifying gaps in the PCa research funding landscape. The mechanisms offered in FY21 (Table 1) supported research spanning from early discovery to more advanced translational and clinical research. The program continuously analyzes PCRP-funded outcomes to assess the overall progress toward achieving its Mission, Vision, and Overarching Challenges, and revises the investment strategy as needed.



PCRP Portfolio Investment FY18-FY21

2021 Congressional Appropriations, Research Investment, and Withholds and Management Costs

Congressional Appropriations	*Research Investment*		*Withholds and Management Costs*	
$110M	Clinical Consortium Award	$7,540,566	USAMRDC	$2,126,640
	Data Science Award	$10,942,607	SBIR/STTR	$3,668,000
	Early Investigator Research Award	$8,014,638	Mgt Costs (4.31%)	$4,492,832
	Health Disparity Research Award	$8,415,318		
	Health Equity Research and Outcomes Improvement Consortium Award	$6,398,457		
	Idea Development Award	$43,700,619		
	Physicians Research Award	$5,310,256		
	Translational Science Award	$7,855,104		
	Modification to ongoing awards	$1,369,058		
Total: $110M		**Total:** $99,546,623		**Total:** $10,287,472

OVERARCHING CHALLENGES

Since the release of its inaugural Strategic Plan in 2018, the PCRP has focused its investments on four Overarching Challenges. The PCRP offers a variety of funding mechanisms that help drive research forward from different approaches, and investments are impacting prostate cancer patients and helping to advance the mission of the PCRP.

ADVANCE health equity and reduce disparities in PCa

IMPROVE quality of life to enhance outcomes and overall health and wellness for those impacted by PCa

DEFINE the biology of lethal PCa to reduce death

1997

Closing the Gap and Reducing Disparities

The PCRP has invested more than $191M in research to improve understanding of and resolve PCa health disparities. Results of the more than 325 PCRP-funded disparity-focused projects, such as those featured here, have contributed to knowledge that is reducing mortality rates and closing the disparate gap between African American (AA) and Caucasian American (CA) men.

2002

North Carolina-Louisiana Prostate Cancer Consortium[1]

The largest population-based study ever conducted followed newly diagnosed AA and CA men for 5 years post-diagnosis. The consortium team discovered racial differences can be attributed to a weak relationship of AA men with the American health care system, as well as the financial burden experienced disparately by AA men. The PCaP develops a large biorepository accessible for the PCa research community.

2005

Positive Influence of Engaging Female Partners[2]

Targeting the partners of high-risk men with informational brochures can be effective to influence health care screening and decision-making.

2014

Patient Education Support Needed[3]

While diagnostics such as gene expression profiling can help inform patients on safe treatment decisions such as active surveillance (AS), results indicate men with low health literacy do not understand diagnoses and treatment options, thus are more likely to choose aggressive treatments over AS.

2017

Improving National Guidelines for Clinical Care – Active Surveillance for Black Men[4]

Black men are more likely to experience disease progression at lower rates of prostate-specific antigen (PSA) change over time, demonstrating both a useful clinical tool to monitor men on AS, and that Black men may benefit from increased frequency of PSA testing compared to white men.

2021

Continued Investments in Health Disparities and Health Equities

The PCRP released the inaugural Health Equity Research and Outcomes Improvement Consortium (HEROIC) Award. Two international teams of funded investigators will incorporate innovative and translational approaches with the potential to make a major impact on advancing health equity, reducing disparities, and improving the quality of life for those impacted by PCa.

2000–2019

47.4% Decrease in Mortality in AA Men

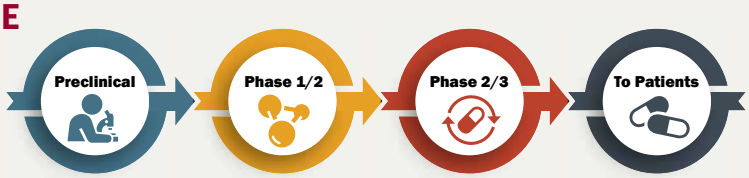
10% Decrease in Mortality Rate Disparity Between AA and CA men

[1] *DAMD17-03-2-0052*
[2] *W81XWH-06-1-0099*
[3] *W81XWH-15-1-0533*
[4] *W81XWH-18-1-0362*

DEVELOP treatments that improve outcomes for men with lethal PCa

PCRP CLINICAL PIPELINE

The PCRP has invested in the discovery and development of multiple therapies and diagnostic tools since the beginning of the program, many of which have continued to advance through the clinical pipeline.



9 products in development | **27** products in development | **3** products in development | **12** products fielded

RARE CANCERS RESEARCH PROGRAM

FOCUS AREAS

- Identify disease-defining molecular pathways, cell context, and microenvironment.
- Develop and validate rare tumor-specific models that can support clinical trial readiness.
- Identify novel therapeutic strategies, including drug repurposing.
- Develop platforms (such as repositories, databanks, and patient registry longitudinal studies) for multiple rare cancers to allow sharing of data, bio-specimens, and resources.

Scan me to access even more information about the program.

VISION

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

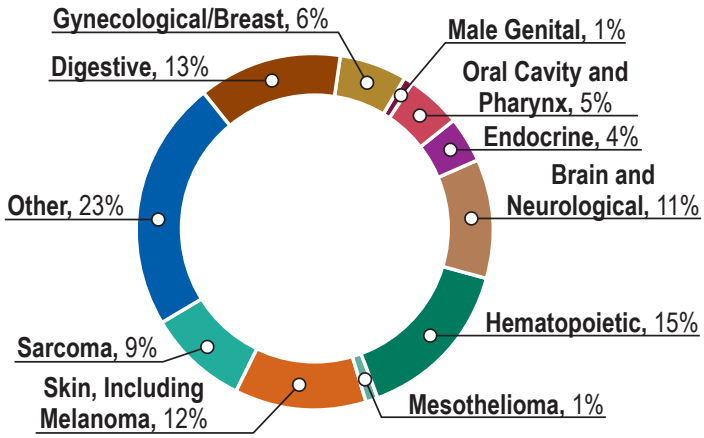
MISSION

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

PROGRAM HISTORY

The CDMRP's Rare Cancers Research Program (RCRP) defines rare cancers as cancers affecting less than 6 per 100,000 individuals annually in the U.S. Based on this definition, there are over **200 types of rare cancers, accounting for 20%-25% of all cancer** diagnoses. Compared to common cancer, relative survival is reduced for patients with rare cancers. **Around 67% of cancers that disproportionately impact the military are rare cancers.** Data from 2017 suggest that there are approximately 8,000 new cases of rare cancers per year in the VA. Rare cancers pose unique challenges to patients, clinicians, and researchers because of limited resources, information, therapeutics, and in-depth knowledge. Research on rare cancers is hindered specifically by lack of available patient tissues, cells, and tumor models; 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.

The RCRP was established in FY20 by Congress. Appropriations for the RCRP from FY20 to FY21 totaled $25M, and the FY22 allocation is $17.5M.

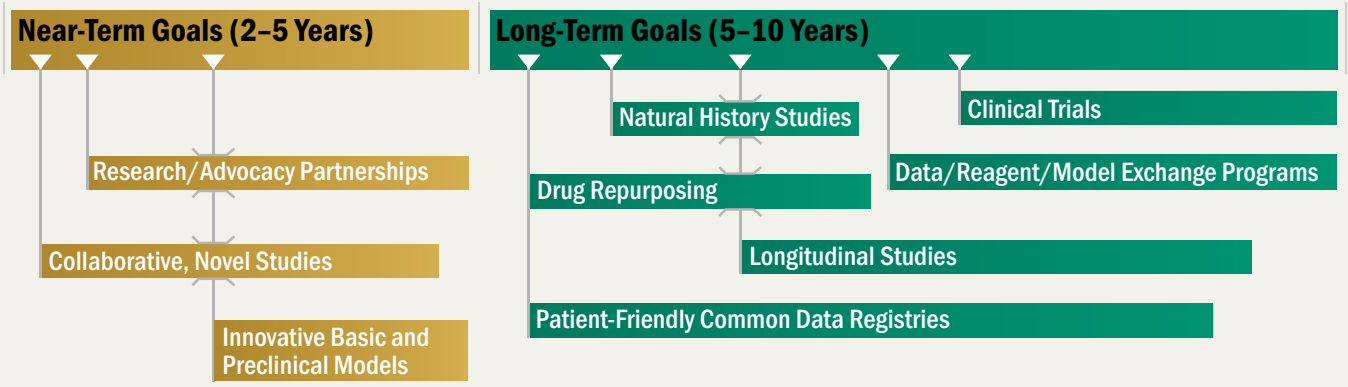


RCRP Investment by American Cancer Society (ACS) Classification Type FY20-FY21

2021 Congressional Appropriations, Research Investment, and Withholds and Management Costs

Congressional Appropriations	*Research Investment*		*Withholds and Management Costs*	
$17.5M	Concept Award	$3,377,728	USAMRDC	$337,752
	Idea Development Award	$9,865,606	SBIR/STTR	$584,000
	Resource Community Development Award	$2,295,386	Mgt Costs (6.27%)	$1,039,528
Total: $17.5M		**Total:** $15,538,720		**Total:** $1,961,280

RCRP GOALS



RESEARCH HIGHLIGHT

RCRP's Strategy: To Build Partnership Among Stakeholders

Dr. William Foulkes, McGill University Health Centre Research Institute

In FY20, the RCRP funded two Resource Community Development Awards to support the development of resources and platforms that can facilitate collaboration and information sharing within the rare cancers community. Dr. William Foulkes at Research Institute of McGill University Health Centre received one of these awards to bring together clinicians, scientists, patients, and patient advocacy groups to develop a Network for Rare Tumors of the Ovary (NRTO). The NRTO will serve as a central web portal for disease information, research resources, and links to two separate registries specific for rare ovarian tumor types to be developed under this award. In partnership with the Eve Appeal Charity, the Small Cell Ovarian Foundation, and the Katie Oppo Research Fund, the team has already launched the Small Cell Carcinoma of the Ovary, Hypercalcemic Type (SCCOHT) website and registry (https://sccoht-smarca4.ca/index-3.html). This website will collect clinical information and biological samples from patients and allow for open sharing of data and resources. Participant recruitment is currently underway to populate the registry and biobank. The team has also initiated the development of patient-derived xenograft models (PDX) from collected SCCOHT samples. PDX models will become publically available through partnership with the Jackson Laboratory, a nonprofit biomedical research institute and global resource for genetically defined mouse models. A second website and registry for sex cord-stromal tumors is currently under development.

Dr. Kurt Weiss, University of Pittsburgh, Programmatic Panel Member FY20-FY22

"I am a sarcoma survivor, surgeon, and scientist. This unusual combination dictates that I carry solemn responsibilities to advance patient advocacy, clinical care, and transformative research. I am immensely proud to serve on the Programmatic Panel of the RCRP. Additionally, my fellow Panelists and I are grateful that the DOD and CDMRP have chosen to devote their resources to rare cancer research. These diseases, while perhaps not posing the epidemiologic burden of other nehoplasia, are no less traumatic for patients, their families, and their support structures. Sarcomas, like other rare malignancies, are often overlooked. Though they are among the rarest of cancers, sarcomas are overrepresented in both the military and adolescent/young adult populations. The RCRP thus provides not only resources of material support for dedicated rare cancer scientists, but has also become a source of hope for military and non-military patients who are diagnosed with rare malignancies. Through the innovative Research and Community Development Award mechanism, the RCRP enables rare cancer patient advocates to build, leverage, and share their strengths on behalf of rare cancer communities. This comprehensive support of rare cancer scientists, patients, and communities is nothing short of extraordinary."

RECONSTRUCTIVE TRANSPLANT RESEARCH PROGRAM

Scan me to access even more information about the program.

VISION *Reconstructive transplant: An accessible reality and viable choice*

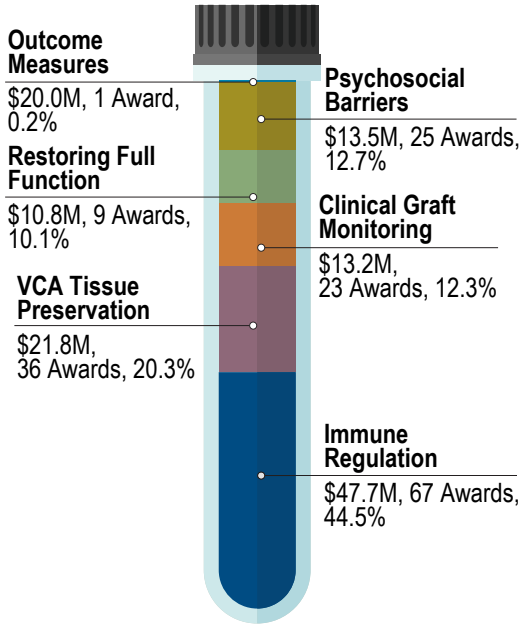
MISSION *Advance science, education, and clinical practice of vascularized composite allotransplantation to improve access and safety and quality of life; implement a standardized and comprehensive approach that encompasses all variables influencing outcomes of VCA for catastrophically injured Service Members, Veterans, and American civilians*

PROGRAM HISTORY

The Reconstructive Transplant Research Program (RTRP) was initiated in FY12 to provide support for research to refine approaches for and increase access to reconstructive transplants and state-of-the-art immunotherapy. The RTRP challenges the scientific community to design innovative research that will expand reconstructive options for catastrophic tissue injury by developing a standardized conduct of vascularized composite allotransplantation (VCA) procedures (e.g., face or hand transplant). Appropriations for the RTRP from FY12 through FY21 totaled $117M. The FY22 appropriation is $12M.

RTRP FY22 FOCUS AREAS

- Reduce the risks of VCA-associated immunosuppression
- Identify and/or validate reliable non-invasive prognostic/diagnostic biomarkers, methods, or tools for monitoring VCA graft rejection
- Develop VCA-specific outcome measures
- Advance existing tissue preservation strategies to extend the timeline between procurement and transplantation
- Standardize and assess protocols and/or clinical practice guidelines for both face and hand transplantation: patient inclusion/exclusion criteria, patient education, surgical procedures, immunosuppression and/or immunoregulation, outcome metrics, quality of life measures, rehabilitation, patient reporting.



RTRP Investment by Barrier FY12-FY20

2021 Congressional Appropriations, Research Investment, and Withholds and Management Costs

Congressional Appropriations	*Research Investment*		*Withholds and Management Costs*	
$12M	Advanced Technology Development Award	$3,998,927	USAMRDC	$232,000
	Investigator-Initiated Research Award	$6,843,805	SBIR/STTR	$400,000
	Remaining Prior Year Obligations	$2,450	Mgt Costs (4.6%)	$522,818
Total: $12M		**Total:** $10,845,182		**Total:** $1,154,818

RESEARCH HIGHLIGHTS

Mapping the Inflammatory Response to VCA

Dr. Yoram Vodovotz, University of Pittsburgh, and Dr. Vijay Gorantla, Wake Forest

Face and hand transplant recipients must take medication to prevent graft rejection. Drs. Vodovotz and Gorantla received an FY14 RTRP award to study the interactions of different VCA tissue types with the immune system. They sought to unravel these interactions using a systems biology approach, which unravels complex interactions by looking at the big picture. By analyzing known inflammatory mediators, the team was able to build maps of inflammatory networks from the skin, muscle, and blood samples in a rat model of VCA. They also identified several key inflammatory mediators in these tissue types in human VCA recipients receiving the immunosuppressant tacrolimus. Together, this data generated a "virtual animal" model which can be used to define the hallmarks and functional mediators of inflammation in VCA and identify markers for early detection and targeted treatment of acute rejection.

Harnessing Single-Cell Technologies to Understand and Diagnose Rejection in VCA

Dr. Rachael Clark and Dr. Bohdan Pomahac, Brigham and Women's Hospital, Harvard Medical

Face and limb transplantation is a transformative reconstructive option for traumatic injury, but is not without risk. Graft rejection can occur even with immunosuppression. Dr. Clark's team received an FY17 RTRP award to study the biological processes underlying rejection in face transplant recipients. Skin biopsy samples from seven face transplant recipients taken at times of non-rejection (Grade 0) through severe rejection (Grade 3) were studied. The team discovered that in Grade 2, upregulation of tissue injury genes was balanced by an equal and opposite upregulation of immunoregulatory and anti-inflammatory genes. As a result, there was inflammation in the skin but no tissue injury. In Grade 3, the balance shifted toward tissue injury. A comparison of the genes upregulated in VCA versus solid organ (kidney, heart) rejection identified genes unique to VCA rejection, including 10 immunoregulatory genes. Understanding these immunoregulatory pathways could lead to novel therapies and minimize the need for immunosuppression.

Use of Donor Lymph Nodes to Promote Graft Tolerance

Dr. Adriano Taddeo, Institute of Virology and Immunology, Mittelhäusern,

The lymphatic system helps protect the body from infection and disease. Its tube-like channels, called lymphatic vessels, transport immune cells and fluid throughout the body to lymph nodes (LNs). Transplantation disrupts lymphatic vessels, and re-establishing these channels is important for graft survival. Dr. Taddeo received an FY16 award to study this process. Hind limb transplants were performed in an animal model either with or without intact donor LNs, and without standard immunosuppressive medications. Results indicate that graft rejection, as well as inflammation, are significantly delayed when transplants include intact donor LNs. In addition, LN transfer was found to increase the donor immune cell population, thereby minimizing the recipient's immune responses to the graft. Together, these data demonstrate the importance of LNs in immune regulation and support the potential of lymphatic-targeted therapies to promote graft tolerance.

Dr. Kimberlee Potter, VA Office of Research Development, Programmatic Panel Member FY16

"I am supportive of the research funded by the RTRP as important and necessary for the advancement of transplantation research beyond immunosuppression and for the widespread adoption of regenerative medicine solutions for our Veterans disfigured by war-related injuries or by lifesaving surgeries."

Dr. Mark A. Wilson, VHA National Surgery Office, Programmatic Panel Member FY20

"The CDMRP RTRP continues to be critical to the evolution of vascularized composite allotransplantation through its stated mission to advance science, education, and clinical practice of VCA to improve access, safety, and comprehensive, standardized assessment of VCA outcomes. The CDMRP RTRP portfolio is unique in its inclusion of basic science, translational, and clinical studies through investigator-initiated research awards and advanced technology development awards. When indicated, VCA provides catastrophically injured Service Members, Veterans, and others the opportunity for improvement of function, form, and appearance."

SCLERODERMA RESEARCH PROGRAM

Scan me to access even more information about the 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 vasculaopathy, 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 disease.

To address the significant research gaps in scleroderma, Congress established the Peer Reviewed Scleroderma Research Program (SRP) in FY20 and FY21, with an annual appropriation of $5.0M. The program was not funded in FY22. In the program's two years, SRP funded a total of 21 awards representing 11 unique projects addressing a subset of Overarching Challenges facing the scleroderma community by funding research to address the Focus Areas below:

Overarching Challenges

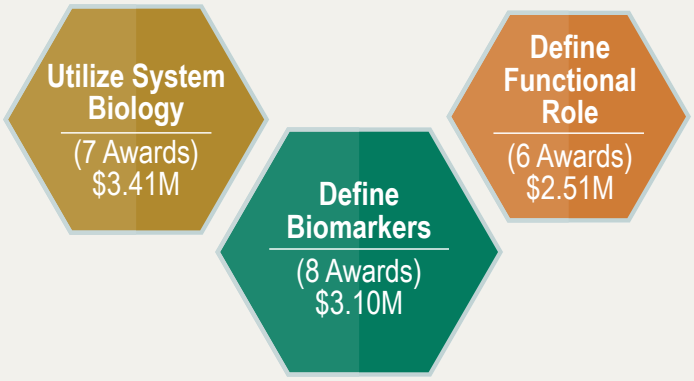
- Understanding Cell Biology
- Understanding Disease Heterogeneity
- Identifying Prognostic and Therapeutic Targets
- Conducting Clinical Trials
- Addressing Quality of Life and Survivorship

Focus Areas

- Define biomarkers ('omics and/or molecular markers, cell subsets, imaging, patient-reported outcomes) that help inform therapeutic choices (immunosuppressive/anti-fibrotic) or predict course (morbidity) and quality of life.
- Utilize systems biology, multi-omics, and preclinical screening approaches (including but not limited to high-throughput screens, the development of animal models, 3D tissue culture and/or organoids) with the intent to develop drug-testing models in order to understand the heterogeneity of disease as well as to develop prevention and therapeutic interventions.
- Conduct studies of diverse populations to include the development of cohorts and identification of potential measures of patient outcomes to understand the unique burden of disease.
- Define functional role of epigenetic changes, multiple cell types, and molecules that mediate pathogenesis and/or initiate or propagate organ-specific disease activity using preclinical models and clinical samples.
- Develop and validate short- and long-term organ-specific and composite clinical outcomes measures to determine treatment efficacy.
- Conduct population-based or cohort studies to understand the prevalence, heterogeneity, and course of this disease, its manifestations, and its impact on health outcomes and activities for daily living.
- Understand and improve the impact of disease and its treatment on the patient's experience and quality of life.

2021 Congressional Appropriations, Research Investment, and Withholds and Management Costs

Congressional Appropriations	*Research Investment*		*Withholds and Management Costs*	
$5M	Idea Development Award	$471,368	USAMRDC	$96,660
	Idea Development Award – Collaboration Option	$1,327,097	SBIR/STTR	$167,000
	Translational Research Partnership Award	$2,772,875	Mgt Costs (3.48%)	$165,000
Total: $5M		**Total:** $4,571,340		**Total:** $428,660



SRP Portfolio Investment by Focus Area FY20-FY21

Nikhil Bhat, Scleroderma Foundation, Consumer Peer Reviewer FY21

"Joining the CDMRP review process was at once intimidating, inspiring, and exciting. I was grateful for the opportunity to provide a voice for scleroderma patients in the scientific review process. As a first-time consumer reviewer in 2021, I was taken aback by the depth of new scientific knowledge about causes and effects of systemic sclerosis, and I hoped I could add something useful to the discussion."

SRP RESEARCH HIGHLIGHTS

Utilize Systems Biology

Idea Development Award

A Novel 3D Scleroderma Skin Model to Test Therapeutic TRPC6 Modulation

Dr. Karin Wuertz-Kozak, Rochester Institute of Technology

Therapeutic testing for dermal fibrosis, a characteristic of scleroderma, in animal models is expensive and inefficient, and currently there are no well-defined 3D skin models for the disease. Dr. Wuertz-Kozak plans to develop a 3D multi-cell skin model to better assess therapeutic targets for dermal fibrosis. In addition, using that model, she will investigate TRPC6, previously shown to increase collagen production and lead to fibrosis, as a therapeutic target in scleroderma.

Define Functional Role

Idea Development Award – New Investigator Collaboration Option

ETV2 Dysregulation in Scleroderma Endothelial Cells

Dr. Pei-Suen Tsou, University of Michigan
Dr. Amr Hakam Sawalha, University of Pittsburgh

Endothelial cell (EC) dysfunction is believed to play an important role in the pathogenesis of SSc. Previous work demonstrated decreased chromatin accessibility and increased expression of chromatin binding transcription factors, such as ETV2, in SSc ECs. Drs. Tsou and Sawalha plan to investigate genes targeted by ETV2 and the relationship to EC cell dysfunction in SSc.

Define Biomarkers

Translational Research Partnership Award

Predicting Response to Treatment in Systemic Sclerosis-Related Interstitial Lung Disease in a Multicenter Observational Cohort

Dr. Shervin Assassi, University of Texas Health Science Center at Houston
Dr. Elana Bernstein, Columbia University Medical Center
Dr. Wenjin Zheng, University of Texas Health Science Center at Houston

Mycophenolate mofetil (MMF), an immunosuppressive drug, has been shown to be effective in treating interstitial lung disease (ILD) for a subset of SSc patients. In a previous DOD-funded project, the investigators identified predictive serum biomarkers for the course of ILD. Drs. Assassi, Bernstein, and Zheng plan to leverage CONQUER, a multisite cohort of SSc patients, to validate a model that predicts response to MMF based on these previously identified biomarkers.

SPINAL CORD INJURY RESEARCH PROGRAM

On average, someone in the U.S. suffers an SCI every 30 minutes.

Roughly 20% of all people in the U.S. with SCI receive care from the VA.

Scan me to access even more information about the program.

VISION

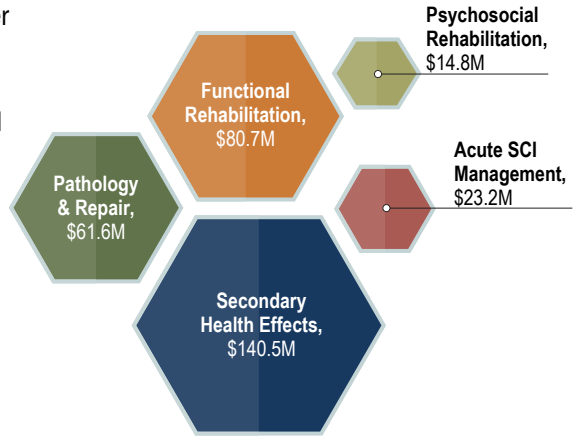
Advance the treatment and management of spinal cord injury and ameliorate its consequences relevant to injured Service Members

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

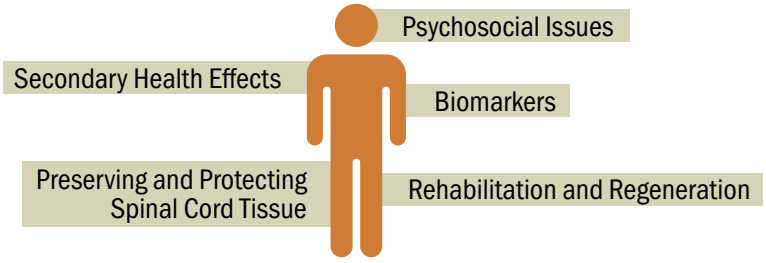
Congress established the Peer Reviewed Spinal Cord Injury Research Program (SCIRP) in FY09 to support research and treatments into repairing/regenerating damaged spinal cords and improving long-term care of those living with an injury. With $397.85M in congressional appropriations between FY09 and FY22 for peer-reviewed spinal cord research, the SCIRP supported 307 awards developing, translating, and optimizing health care solutions across the continuum of care from management of the acute injury through functional and psychological rehabilitation for chronically injured individuals. Historically, the program invests most heavily into research addressing secondary health effects of spinal cord injury (SCI) such as bladder/bowel dysfunction and pain.



SCIRP Investment FY09-FY21

CURRENT PROGRAM PRIORITIES

The program evaluates its priorities annually, in partnership with members of the SCI community, researchers, clinicians, and other funders. The FY22 program priorities are listed below:



2021 Congressional Appropriations, Research Investment, and Withholds and Management Costs

Congressional Appropriations	*Research Investment*		*Withholds and Management Costs*	
$40M	Clinical Trial Award	$10,614,340	USAMRDC	$773,320
	Expansion Award	$6,315,335	SBIR/STTR	$1,334,000
	Investigator-Initiated Research Award	$7,053,952	Mgt Costs (3.28%)	$1,243,344
	Translational Research Award	$12,665,709		
Total: $40M		**Total:** $36,649,336		**Total:** $3,350,664

EXCITING RESEARCH OUTCOMES

The following are examples of research findings from 2022 with great promise to improve the health and well-being of people living with SCI.

Drug Interventions

Drug-induced hypothermia has a similar neuroprotective effect with a more clinically feasible administration to physical hypothermia, making it a promising pre-hospital therapy for acute SCI management. *University of Maryland, Baltimore*

Bromodomain and Extra-Terminal protein inhibitors, when administered within 24 hours of injury, lessened inflammation and significantly reduced lesion size in a rat model of SCI, promoting repair and protection of spinal cord tissue after injury. *University of Miami, Coral Gables*

Surgical Interventions

A decision support intervention related to nerve and tendon transfer surgery post-SCI was developed to better inform individuals of their options around these surgical interventions. Limited upper extremity function is a major barrier to independent living, and improvement to hand and arm function can greatly improve quality of life for people living with high cervical SCIs. *Washington University*

Device Interventions

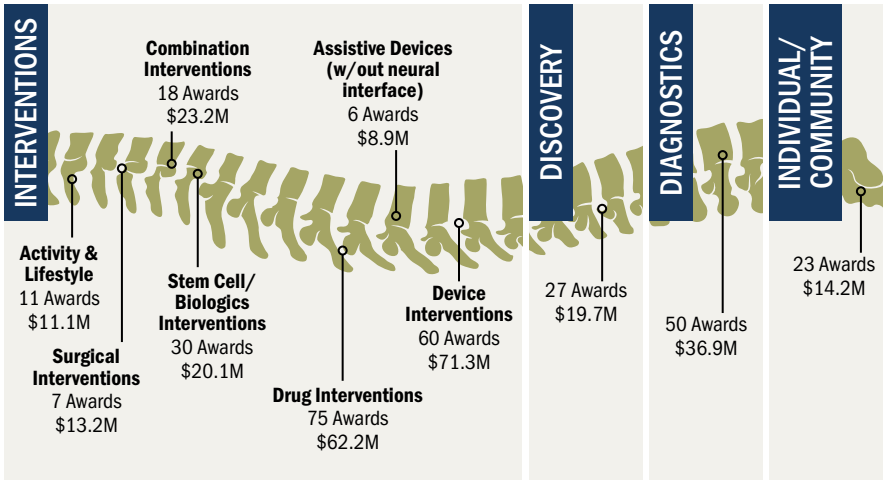
A combination therapy of functional electrical stimulation paired with an implanted brain computer interface restores both coordinated reaching and grasping movements in enrolled participant with cervical SCI. Further investigation will evaluate restoration of touch sensation in this same participant. *Case Western Reserve University*

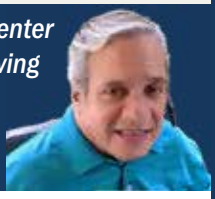
Acute intermittent hypoxia (AIH), or brief periods breathing low oxygen, improves respiratory function in adults with SCI. Functional benefits of AIH may be enhanced by combination with task-specific breathing exercises, advancing translation of this simple, low-cost, non-invasive therapy into clinical practice. *University of Florida*

Cell Interventions

Leveraging bladder grafts derived from patients' own cells and blood vessels improves bladder graft size and function in a pig model. This state-of-the-art technique will lead to clinical studies in humans and may ultimately result in a new surgical option for patients who need bladder augmentation post-SCI. *University of California, Davis*

INTERVENTION INVESTMENT BY CATEGORY (FY09-FY21)





Hector Del Valle, Center for Independent Living – Central Florida, Consumer Peer Reviewer FY20

"In 2021, I had the honor of serving as a consumer reviewer for the SCIRP. I found it to be the most rewarding work that I've done in a long time. This panel included individuals with lived experience, like myself, along with scientists, and together we evaluated applications that could have a great positive impact on the SCI community. I felt valued and appreciated, and can certainly attest to the difference you make as a consumer reviewer. Consumer reviewers are able to speak to the implications an application may have on daily life, as well as the life cycle, for persons with SCI – that might otherwise go unnoticed by scientists."

IMPACTFUL NEW RESEARCH

Targeted Spinal Cord Plasticity for Alleviating SCI-Related Neuropathic Pain – *Medical University of South Carolina and Washington University in St. Louis – School of Medicine*

Serum Biomarkers for Classifying Injury Severity and Predicting Outcome After Acute Spinal Cord Injury – *University of British Columbia*

Accelerating Translation of a Small-Molecule KCC2 Enhancer to Promote Recovery and Reduce Neuropathic Pain After SCI Using a Pig Model – *University of Utah and AXONIS*

Development and Validation of a Nutrition Knowledge Questionnaire for Individuals with Spinal Cord Injuries and Disorders – *VA Medical Center, Memphis, TN*

TICK-BORNE DISEASE RESEARCH PROGRAM

Scan me to access even more information about the program.

VISION

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

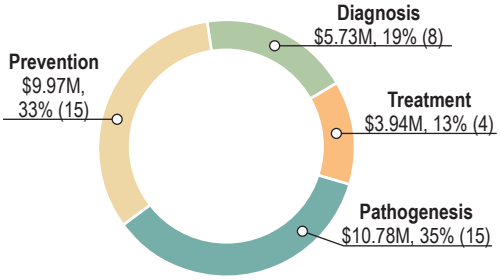
MISSION

To understand the pathogenesis of Lyme disease and other tick-borne illnesses and conditions, 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

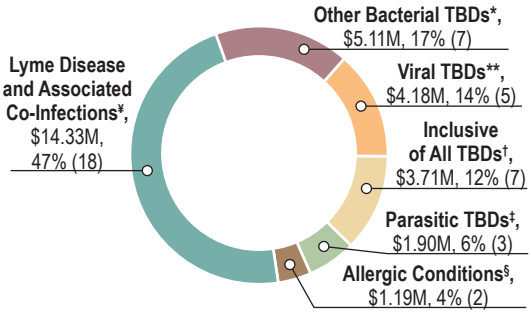
PROGRAM HISTORY

The Tick-Borne Disease Research Program (TBDRP) was established in FY16 due to the efforts of Lyme disease advocates. The TBDRP has received a total of $34M in congressional appropriations from FY16-FY21 and aims to support research to improve capabilities in tick-borne disease (TBD) prevention, diagnosis, and treatment.

As tick populations increase and expand geographically, new tick-borne pathogens and associated diseases/conditions continue to emerge.[1] Unfortunately, TBDs often go undiagnosed, or misdiagnosed, which can interfere with administering appropriate treatment. The study of TBDs is complicated by the breadth of conditions that result from infection with various bacterial, viral, and parasitic pathogens, and because a single tick bite can transmit more than one pathogen at a time. TBDs and conditions can negatively impact multiple body systems and have long-term health implications. To improve TBD diagnosis and subsequent treatment for civilian and military populations, more sensitive and accurate diagnostic tests are needed, as well as better understanding of the mechanisms behind these various infections and long-term effects on health. The TBDRP strives to address these fundamental knowledge gaps in the field of TBDs.



TBDRP Portfolio By Research Focus FY16-FY21 (42 Awards)



TBDRP Portfolio by Disease/ Condition FY16-FY21 (42 Awards)

¥ "Lyme disease and associated co-infections" refers to studies of Lyme disease alone or with various co-infections commonly diagnosed with Lyme disease. 50% of these awards directly investigate or have implications in Post-Treatment Lyme Disease Syndrome (PTLDS), or persistent/chronic symptoms of Lyme disease.
* Currently includes Rickettsiosis and Ehrlichiosis
** Currently includes Powassan, Crimean-Congo Hemorrhagic Fever, and Tick-Borne Encephalitis viruses
† Indicative of studies involving approaches applicable to any/all TBDs
‡ Currently refers to Babesiosis
§ Currently refers to Alpha-Gal Syndrome

[1] https://www.cdc.gov/media/dpk/diseases-and-conditions/lyme-disease/index.html.

2021 Congressional Appropriations, Research Investment, and Withholds and Management Costs

Congressional Appropriations	*Research Investment*	*Withholds and Management Costs*
$7M	Career Development Award.....$908,763	USAMRDC $135,320
	Idea Development Award $5,302,613	SBIR/STTR $234,000
	Modification to ongoing awards $15,000	Mgt Costs (6.1%)..... $404,304
Total: $7M	**Total:** $6,226,376	**Total:** $773,624

MILITARY RELEVANCE

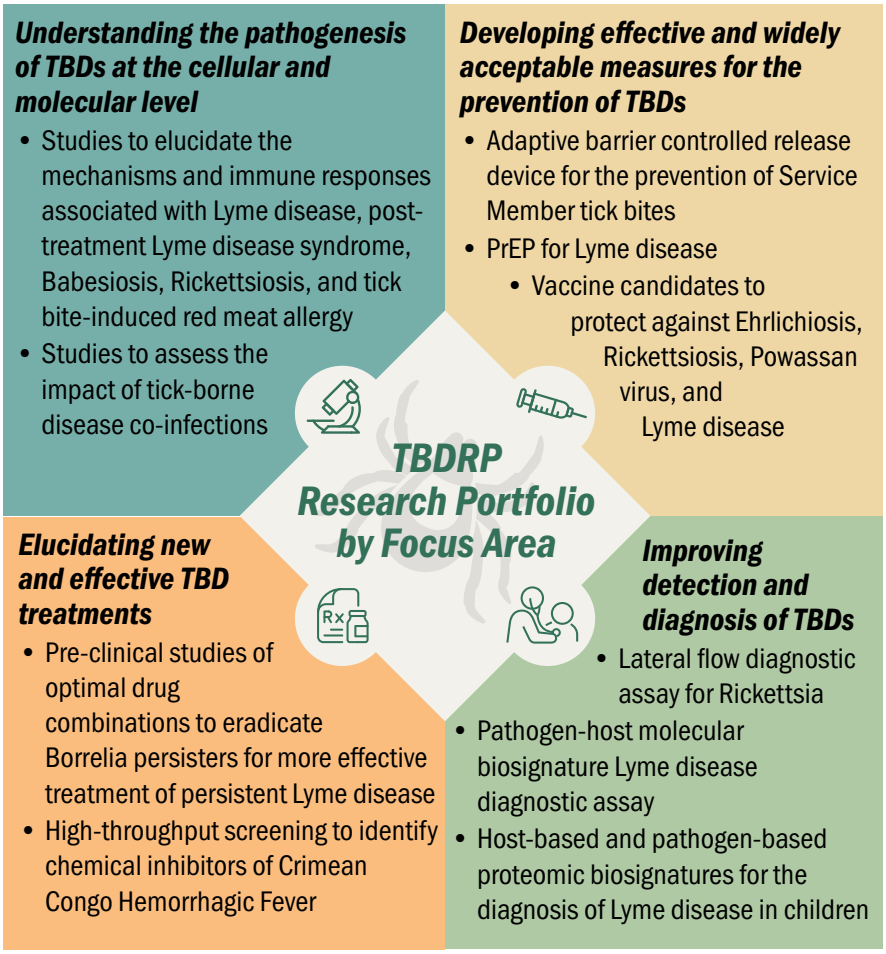
- Approximately 6,000 active-duty Service Members and nearly 56,000 Service Member beneficiaries were diagnosed with a reportable TBD between 2006–2020.[1]
- Lyme disease accounted for ~80% of TBDs diagnosed in Service Members and their beneficiaries between 2006–2020.[1]
- Lyme disease accounted for ~44% of all reportable medical event cases of vector-borne diseases (VBD) (confirmed, probable, and suspected), and Lyme was the most common of the VBDs reported from 2016–2020.[2]

RESEARCH HIGHLIGHTS

Development of a Bactericidal, Long-Half-Life, OspA-Specific Human Monoclonal Antibody as a Novel Pre-Exposure Prophylaxis (PrEP) for Lyme Disease

Dr. Yang Wang, University of Massachusetts Medical School

Current Lyme disease prevention strategies rely heavily on physical barriers and the use of tick repellents, which require compliance and reapplication. Service Members' primary line of defense from tick bites is the use of permethrin-treated uniforms, which become less effective as potency wanes with washing. With funding from a TBDRP Investigator-Initiated Research Award, Dr. Yang Wang and her team of experts from MassBiologics are developing a pre-exposure immunoprophylaxis, or PrEP, for Lyme disease prevention. With the use of human monoclonal antibodies, the PrEP offers a longer window of protection from infection by Lyme disease-causing bacteria versus traditional vaccines. A single dose of human antibody PrEP could act as an additional barrier of protection from Lyme disease, benefiting Service Members, their beneficiaries, and the American people. Results from this TBDRP-funded effort helped to advance PrEP along the pathway to FDA approval, with an Investigational New Drug application approved this year and a phase 1 clinical trial now underway for the lead candidate.



Wendy Adams, Bay Area Lyme Foundation, Programmatic Panel Member FY20-FY22

"I really appreciate the opportunity to serve on CDMRP because of its focus on innovation and impact for patients. High-risk, high-reward research is crucial to fund, because we need vastly improved diagnostics and treatments for both Lyme and other tick-borne diseases."

[1] Data from the Armed Forces Health Surveillance Branch (AFHSB); [2] AFHSB Feb 2021 Medical Surveillance Monthly Report

TOXIC EXPOSURES RESEARCH PROGRAM

VISION

Minimize and mitigate the impact of military-relevant toxic exposures and improve the quality of life of those affected

MISSION

Support innovative and impactful research aimed at identifying and understanding the pathological mechanisms, outcomes and comorbidities associated with toxic exposures in order to facilitate the prevention, diagnosis, and treatment of the invisible and visible diseases and symptoms that are associated with toxic effects impacting Service Members, Veterans, and the American public

PROGRAM HISTORY

The Toxic Exposures Research Program (TERP) was established in FY22 with a congressional appropriation of $30M to support research focused on four main Topic Areas: (1) neurotoxin exposure, (2) Gulf War illness (GWI) and its treatment, (3) airborne hazards and burn pits, and (4) other military service-related toxic exposures in general, including prophylactic medications, pesticides, organophosphates, toxic industrial chemicals, materials, metals, and minerals. The FY22 congressional language focuses on the need to improve the scientific understanding and pathobiology from exposures, more efficiently assess comorbidities, and speed the development of treatments, cures, and preventions. The CDMRP has previously received congressional support for research aimed at providing health care solutions for some of the diseases/conditions linked to toxic exposures, including the Peer Reviewed Gulf War Illness Research Program (GWIRP), the PRMRP Burn Pits and Metals Toxicology Topic Areas, and the Peer Reviewed Neurotoxin Exposure Treatment Parkinson's Research Program (NETP).

MILITARY RELEVANCE

Toxic exposures are known and unknown potentially harmful substances that Service Members are exposure to as part of their military service. Over 3.7 million U.S. Service Members have participated in operations in the Southwest Asia Theater of Military Operations and Afghanistan since 1990,[1] and individuals who served in that region were likely to have been exposed to a number of toxic agents including, but not limited to, emissions from open burn pits, dust and sand suspended in the air, industrial pollution, sarin, pyridostigmine bromide, oil-well fire smoke, and vehicle exhaust. While many exposures are associated with deployment environments, other exposures including, but not limited to, paints, fuels, exhausts, and contaminated water also occur in non-deployment settings. Neither the short- nor long-term effects of toxic exposures are well-defined and, in many cases, identifying a particular exposure can be challenging. Moreover, correlating diseases, conditions, and symptoms to a particular operational environment, exposure, or series of exposures poses additional challenges. While many toxic exposures have been identified, there are likely unknown exposures or mixtures of exposures that have not even been identified yet, and the relationship of these exposures to health outcomes such as GWI, respiratory, neurologic, and cardiac diseases and conditions, sleep disturbances, and cancers (to name a few) remain poorly understood.

FY22 TERP DEVELOPMENTS

The TERP released a request for information (RFI) and held an inaugural Stakeholders meeting, during which individuals with relevant experience and expertise came together to identify knowledge gaps, targeted outcomes, and patient needs as they pertain to the four FY22 TERP Topic Areas. A summary of the outcomes from the TERP Stakeholders meeting can be found on the TERP website. Following the Stakeholders meeting, the TERP assembled a Programmatic Panel of expert scientists, clinicians, and consumer advocates who reviewed the congressional language, research landscape, and outcomes of the RFI and Stakeholders meeting to develop the TERP's FY22 Vision, Mission, Program Goals, Focus Areas, and Investment Strategy.

Scan me to access even more information about the program.

[1] National Academies of Sciences, Engineering, and Medicine. 2020. Respiratory health effects of airborne hazards exposures in the Southwest Asia Theater of Military Operations. Washington, DC: The National Academies Press. https://doi.org/10.17226/25837

PROGRAM GOALS

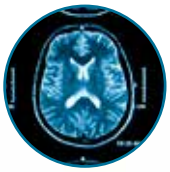
Elucidate mechanisms of how toxic exposures result in adverse effects, including, but not limited to, toxicities, malignancies, neurologic and respiratory disorders, cardiac complications, sleep disorders, immune system dysfunction, gastrointestinal issues, etc.

Diagnose the effects of toxic exposures, understand the phenotypic/genotypic and clinical outcomes associated with short-term and long-term exposures and predict disease progression.

Predict and prevent toxic exposures by identifying strategies that can anticipate, identify, monitor and prevent Service Members and the American public from adverse effects of exposures to toxic substances.

Develop therapeutics, treatments and strategies to minimize symptoms and disease progression associated with toxic exposures.

TOPIC AREAS



Neurotoxin Exposure

Gulf War Illness and Its Treatment

Airborne Hazards and Burn Pits

Other Military Service-Related Toxic Exposures in General

Including Prophylactic Medications, Pesticides, Organophosphates, Toxic Industrial Chemicals, Materials, Metals, and Minerals

Retired U.S. Air Force Tech. Sgt. Jennifer Burch, Wounded Warrior Foundation, Programmatic Panel Member FY22

"As a consumer for the TERP, I'm inspired by the opportunity to improve the field of research for our nation's Service Members who were exposed to toxic substances such as burn pits while serving our country. The war may be over, but the war combating the health and wellness ramifications of the war has just begun. The severity of these conditions will become more visible as time goes on, just like they did for Vietnam Veterans and Veterans from every other war. The TERP has the ability to fund research that will provide life-saving results."

FY22 FUNDING MECHANISMS

TRAUMATIC BRAIN INJURY AND PSYCHOLOGICAL HEALTH RESEARCH PROGRAM

Scan me to access even more information about the program.

VISION

Optimize the prevention, assessment, and treatment of psychological health conditions and/or traumatic brain injuries

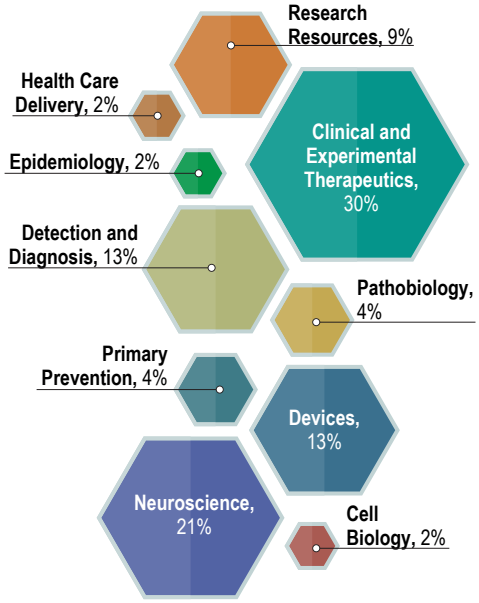
MISSION

Fund research to understand, prevent, assess, and treat psychological health conditions and/or traumatic brain injuries that accelerates solutions to improve health, well-being, and health care of Service Members, DOD beneficiaries, Veterans, and the American public

PROGRAM HISTORY

The U.S. Congress appropriated funds for TBI and psychological health medical research in FY07 in response to the devastating impact of psychological health conditions and TBIs on our Service Members and their families. Congressional appropriations to date total over $2.2B, including the FY22 appropriation of $175M.

Through the Traumatic Brain Injury and Psychological Health Research Program (TBIPHRP), research Focus Areas and relationships, the program is uniquely positioned to fund research for the benefit of our Service Members, Veterans, and their families. The program acknowledges that physical trauma and psychological trauma do not occur in isolation. As such, the TBIPHRP funding opportunities allow for "whole person" research that considers both psychological health and TBI outcomes in the same proposal. The TBIPHRP leverages relationships with the lived experience subject matter experts (consumers) and DOD/non-DOD agencies to share information, eliminate research overlap, and identify areas of synergistic complementation. This input was used to align the TBIPHRP Focus Areas with real clinical needs. Taken together, this allows the TBIPHRP-funded research to have a higher potential for impact, relevance, and transition to clinical practice.



TBIPHRP Investment by Research Type FY21

2021 Congressional Appropriations, Research Investment, and Withholds and Management Costs

Congressional Appropriations	*Research Investment*	*Withholds and Management Costs*
$175M	Clinical Research Development Award ..... $599,636 Clinical Trial Award ..... $66,419,081 Focused Program Award ..... $53,732,513 Idea Development Award ..... $4,180,898 Investigator-Inititated Research Award ..... $9,989,600 Translational Research Award $23,586,866	USAMRDC ..... $3,383,260 SBIR/STTR ..... $5,837,000 Mgt Costs (4.39%) $7,271,146
Total: $175M	**Total:** $158,508,594	**Total:** $16,491,406

Neuroimmunoendocrine Interface: Exploring a Unifying Axis for Precision Care in PH and TBI (NEXUS)

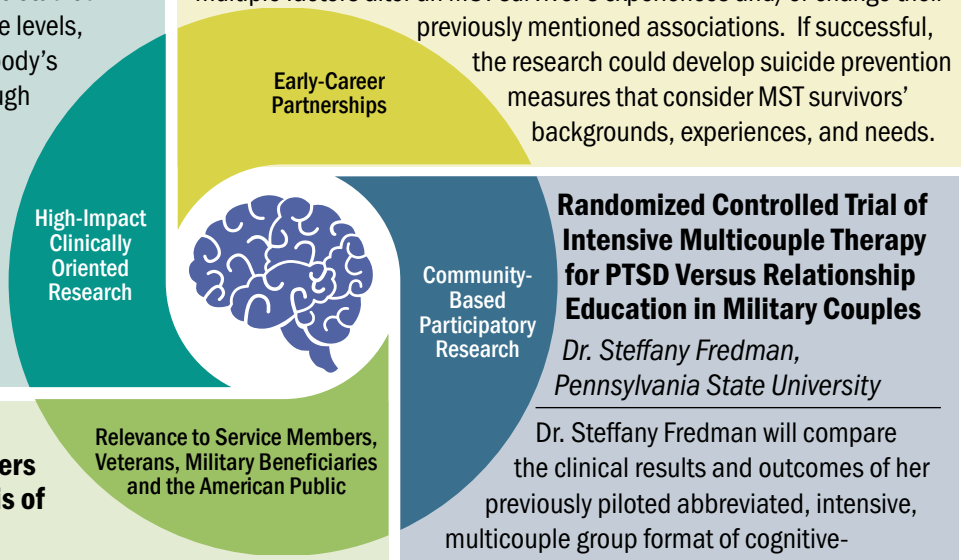
Dr. Amy Wagner, University of Pittsburgh

Dr. Amy Wagner and her team are studying how a person's biology, stress, and resilience to stress can affect recovery after TBI and subsequent risk for psychological health conditions. These nuisances will be studied through blood protein and hormone levels, which naturally fluctuate with the body's response to stress, as well as through the examination of an individual's genetic composition. Anticipated results could provide a framework for personalized TBI and PH treatments based on an individual's stress hormone levels.

Preventing Suicide Among Survivors of Military Sexual Violence: Identifying Critical Risk Periods and Factors That Attenuate and Exacerbate Risk

Dr. Rebecca Blais, Arizona State University
Dr. Lindsey Monteith, Denver Research Institute

Drs. Blias and Monteith are evaluating the relationship between stigma and institutional response to military sexual trauma (MST) survivors' feelings of suicidal ideation and attempt. They will also assess whether multiple factors alter an MST survivor's experiences and/or change their previously mentioned associations. If successful, the research could develop suicide prevention measures that consider MST survivors' backgrounds, experiences, and needs.



Randomized Controlled Trial of Intensive Multicouple Therapy for PTSD Versus Relationship Education in Military Couples

Dr. Steffany Fredman, Pennsylvania State University

Dr. Steffany Fredman will compare the clinical results and outcomes of her previously piloted abbreviated, intensive, multicouple group format of cognitive-behavioral conjoint therapy (CBCT) for PTSD (AIM-CBCT for PTSD) to a similar Prevention and Relationship Enhancement Program, which is widely used in the DOD. If successful, the AIM-CBCT for PTSD could be implemented within the military and VA health systems and to help military and Veteran families maintain strong, healthy relationships.

Quantitative Pupillometry Combined with Blood Biomarkers for the Diagnosis and Prognosis of Mild Traumatic Brain Injury

Dr. Bradley Dengler, Uniformed Services University of the Health Sciences

Dr. Bradley Dengler and his team will assess the collective applicability of pupillary response and blood biomarkers to diagnose mTBI and predict symptom severity and length utilizing two commercially available technologies. Results of this study could potentially produce an easy-to-use device that can be implemented with minimal training at the point of injury to evaluate Soldiers for mTBIs, allowing them to either remain on duty or be evacuated.

Dr. Jeffrey Iliff, University of Washington School of Medicine, Programmatic Panel Member FY21-FY22

"As a member of the TBIPH Program Panel, it has been gratifying to be a part of the process that helps to steer research priorities surrounding brain health among our active-duty Service Members and Veterans. Our understanding of the neuroscience underlying traumatic brain injury and other mental health issues is progressing rapidly. The two-tier review process, including scientific, stakeholder, and consumer input, is unique in balancing the need to advance the leading edge of scientific discovery with leveraging those discoveries for practical impact into the lives and well-being of Service Members."

Dr. Kelley Brix, Defense Health Agency, Research and Engineering Directorate, Programmatic Panel Chair FY21-FY22

"Psychological conditions and traumatic brain injuries continue to be among the most prevalent and most challenging health problems in Service Members. This CDRMP program shows great promise in developing new methods to diagnose these conditions more accurately and developing new, more effective treatments. It's an honor to participate in setting future research priorities and to serve on the programmatic review committee."

TUBEROUS SCLEROSIS COMPLEX RESEARCH PROGRAM

Scan me to access even more information about the program.

VISION

Improve prevention strategies and treatments to lessen the impact of tuberous sclerosis complex while striving for a cure

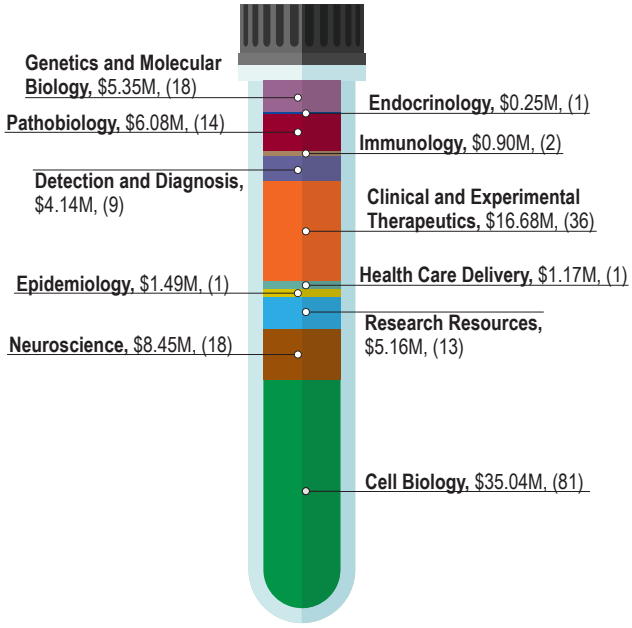
MISSION

Support innovative and high-impact research that promotes discoveries in tuberous sclerosis complex, 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

PROGRAM HISTORY

Tuberous sclerosis complex (TSC) is a rare genetic disorder that affects 1 in 6,000 newborns in the U.S. Currently, 40,000-80,000 individuals in the U.S. and 1 to 2 million individuals worldwide have TSC. The disorder is caused by mutations in either the *TSC1* gene or *TSC2* gene, which encode the proteins hamartin and tuberin, respectively. The mutations result in hyperactivation of the mammalian target of rapamycin (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; however, the most severe ones include seizures, developmental delays, autism, and behavioral problems. There is no cure for TSC.

The Peer Reviewed Tuberous Sclerosis Complex Research Program (TSCRP) was established in FY02 with a congressional appropriation of $1M. Since then, a total of $105M has been appropriated to the program, including $8M in FY22. From FY02 to FY21, the TSCRP has funded 194 awards. Today, the TSCRP is the second largest government funding source for TSC research in the U.S. It has played a critical role in helping accelerate high-impact research, exploring new concepts, encouraging innovation, and bringing new investigators into the TSC field.



TSCRP Portfolio by Research Type FY02-FY21

2021 Congressional Appropriations, Research Investment, and Withholds and Management Costs

Congressional Appropriations	*Research Investment*	*Withholds and Management Costs*
$8,000,000	Clinical Translational Research Award ..... $1,167,408 Exploration – Hypothesis Development Award ..... $1,421,305 Idea Development Award $4,573,311	USAMRDC ..... $154,660 SBIR/STTR ..... $267,000 Mgt Costs (5.49%) $416,316
Total: $8,000,000	**Total:** $7,162,024	**Total:** $837,976

PROGRAM HIGHLIGHTS

Developing Novel mTORC1 Inhibitors to Treat TSC

Dr. Michael Hall, University of Basel, Switzerland

As TSC arises from this unbridled mTORC1 activity, mTORC1 inhibitors (rapalogs) are commonly used to treat several TSC manifestations such as renal, lung, facial, and brain tumors, as well as partial-onset seizures in children. However, over time rapalogs can show limited effectiveness and reduced safety. Since TSC patients need to be treated chronically, developing more effective treatment options for TSC symptoms is of utmost interest and would have a profound impact on TSC patients.

In FY19, Dr. Michael Hall at the University of Basel in Switzerland received an Exploration – Hypothesis Development Award from the TSCRP to investigate novel mTORC1 inhibitors to treat TSC. Over the course of this award, Dr. Hall's group identified a novel, rapalog-unrelated, druggable site on mTORC1 and identified that perturbing this novel site reduces mTORC1's activity. This groundwork could lead to a new generation of selective mTORC1 inhibitors that may uncover novel treatment options for TSC.

Dr. Hall continues to build on this work with additional support from an FY21 TSCRP FY21 IDA. Dr. Hall asserts that, "[t]he clinical potential of these novel compounds is immense and readily testable. We believe our approach could be an important development, as we predict it to be more effective, selective, and safer in the treatment of TSC symptoms. Novel mTORC1-targeted drugs with reduced side effects would greatly improve the health and quality of life of TSC patients."

Autophagy and the Neurocognitive Deficits in TSC

Dr. Guomei Tang, Columbia University Medical Center

Recent evidence suggests that disinhibited mTOR signaling contributes to TSC-related learning and memory deficits. The mTOR inhibitor rapamycin corrects both synaptic and cognitive defects in Tsc1 and Tsc2 heterozygous mutant mice. Clinical trials are thus underway to test the effects of rapamycin analogues on neurocognitive problems in TSC patients. One caveat for rapamycin treatment is that long-term therapy is required to maintain effectiveness, which may cause adverse side effects.

In work funded by an FY15 TSCRP IDA, Dr. Guomei Tang at the Columbia University Medical Center investigated the role of impaired mTOR-dependent autophagy in the neurocognitive deficits in TSC. The team found that within the brain region responsible for learning and memory, synapse maturation and long-term synaptic plasticity were impaired in autophagy-deficient mice. Further, as the mice aged, cognitive deficits became apparent in autophagy-deficient mice. These study results strongly suggested that autophagy is a promising therapeutic target for TSC-associated neuropsychiatric symptoms.

Dr. Tang will follow up this successful FY15 project with a new FY21 TSCRP IDA to investigate autophagy induction as a novel therapeutic strategy for TSC-associated cognitive and autistic social deficits. The goal of this project is to develop a new alternative treatment paradigm for TSC patients. If both preclinical and clinical studies confirm that autophagy induction is an effective intervention for TSC-associated neuropsychiatric symptoms, the findings could rapidly translate into new clinical practices.

FDA-Approved Drug, HYFTOR

The recent FDA approval of HYFTOR™ to treat facial angiofibromas associated with TSC was great news to the TSC community, as there was previously no effective permanent treatment for this condition. The journey of developing a similar drug began over a decade ago with a clinical trial funded by the TSCRP.

2011

The TSCRP funded an early trial led by Dr. Mary Kay Koenig to study topical rapamycin (also known as sirolimus) to treat facial angiofibromas in TSC patients. The goal of the **TREATMENT** trial was to develop a form of rapamycin that could provide a safe, effective treatment for facial angiofibromas in patients with TSC.

2014

The **TREATMENT** trial was completed with a final enrollment of 179 patients.

2018

Dr. Koenig's team published their results, "Efficacy and Safety of Topical Rapamycin in Patients with Facial Angiofibromas Secondary to Tuberous Sclerosis Complex: The **TREATMENT** Randomized Clinical Trial" in *JAMA Dermatology* in 2018.

2022

The FDA approved **HYFTOR™** for facial angiofibromas. **HYFTOR** is the first FDA-approved topical treatment for facial angiofibromas in adults and children 6 years of age or older who have TSC.

VISION RESEARCH PROGRAM

Scan me to access even more information about the 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 DOD Peer Reviewed Vision Research Program (VRP) was established by Congress in 2009 to "target the various causes, effects and treatment of vision injury" as related to military exposure. The VRP has received appropriations totaling $144.95M through FY21 and is the leading funder of research on visual system injury ranging from ocular trauma to visual dysfunction associated with TBI.

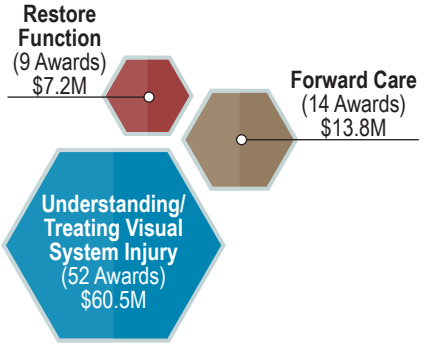
RELEVANCE TO MILITARY HEALTH

Eye injury and visual dysfunction resulting from military exposure affect a large number of Service Members and Veterans. Surveillance data from the DOD showed more than 275,000 eye injuries in the U.S. Armed Services between 2000 and 2017. More than 6,000 of the injuries were categorized as high risk of blindness. In addition, statistics from the Traumatic Brain Injury Center of Excellence show that through the third quarter of 2021, more than 449,000 Service Members have been diagnosed with TBI, which can have significant impact on vision even when there is no injury to the eye.

The VRP challenges the scientific community to design innovative research that will significantly advance the understanding, prevention, diagnosis, mitigation, and/or treatment of eye injury or visual dysfunction associated with military exposure and research that will enable the delivery of care in the military operational environment.

FOCUS AREAS

- Eye injury or visual dysfunction as related to military exposure
- Diagnosis, stabilization, and treatment of eye injuries in austere environments and prolonged field care settings
- Restoration of visual function after military exposure-related vision loss or severe visual impairment



VRP Investment by Focus Areas FY17-FY21

2021 Congressional Appropriations, Research Investment, and Withholds and Management Costs

Congressional Appropriations	*Research Investment*		*Withholds and Management Costs*	
$20M	Clinical Trial Award	$2,237,200	USAMRDC	$386,660
	Investigator-Initiated Research Award	$14,216,162	SBIR/STTR	$667,000
	Translational Research Award	$1,512,511	Mgt Costs (4.16%)	$787,676
	Modification to ongoing awards	$192,791		
Total: $20M		**Total:** $18,158,664		**Total:** $1,841,336

HOT OFF THE PRESS FROM VRP-FUNDED RESEARCH

Dr. Michael Iuvone, Emory University

PMID: 34353120

Traumatic blast injury, such as those caused by improvised explosive devices, is a common cause for vision loss due to damage to the optic nerve and central visual pathway. Dr. Michael Iuvone and his team at Emory University characterized the pathobiology and time course of vision loss in a mouse model of blast injury and investigated the neuroprotective effect of a small molecule, HIOC. They demonstrated that HIOC, an activator of the tropomycin-related kinase B receptor (TrkB, the cognate receptor for brain-derived neurotrophic factor), effectively protected vision when systemically administered within 3 hours after blast. One week of HIOC treatment mitigated vision loss for at least 4 months. These results identify HIOC as a promising candidate for preserving vision after traumatic blast injury.

Dr. Steven Wilson, Cleveland Clinic

PMID: 35074340

Corneal scarring fibrosis is a major contributor to blindness worldwide. Dr. Steven Wilson and his team at the Cleveland Clinic are using a corneal-injured rabbit model to evaluate the effects of Losartan, an angiotensin II receptor antagonist. Specifically, they treated the injured eye with Losartan and evaluated corneal transparency, as well as the expression of collagen IV and transforming growth factor beta. The topical application of Losartan was found to reduce the negative effects of corneal scarring fibrosis, and future work will evaluate this promising drug in a larger animal model.

Dr. Valeria Canto-Soler, University of Colorado, Denver

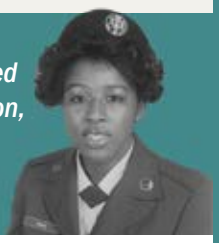
PMID: 35256656

Inherited retinal disorders and dry age-related macular degeneration result in the loss of photoreceptors/vision. New treatments such as gene therapy and cell replacement require monitoring response to light at a cellular level. Dr. Canto-Soler and her team at the University of Colorado, Denver, together with their collaborators at Nanoscope Instruments, have developed an optical coherence tomography-guided micro-focal multicolor laser stimulation and electroretinogram platform to record electrophysiological responses at the cellular level in the retina. Their latest work tested their imaging system in a disease and healthy minipig model with great success, showing function recording of rods and cones.

Dr. Nawajes Mandal, University of Tennessee

PMID: 34365584

TBI causes neuroinflammation and neurodegeneration, leading to visual, motor, and emotional deficits. Dr. Nawajes Mandal and his team at the University of Tennessee demonstrated that mice with elevated levels of systemic N-3 polyunsaturated fatty acid (n-3 PUFA) are resistant to TBI-induced decline in visual/motor functions and depression. This is associated with a blocking of TBI-mediated increase of ceramide, a sphingolipid that induces neuroinflammation and degeneration, in the mouse brains. This study suggests that n-3 PUFA is a promising candidate for preventing TBI-induced neurodegeneration.



Doris Jones, Blinded Veterans Assocation, Consumer Peer Reviewer FY17, FY19-FY21

"I have enjoyed the opportunity to serve as a consumer reviewer for the Vision Research Program the past 3 years; being able to provide input for life-changing research is a rewarding experience. I feel like a valuable member of these peer reviews, and I know what I have to bring to the table matters. It is an honor to give a voice to those living with vision loss and provide insights from lived experience."

RETINA AND OPTIC NERVE INJURY RESEARCH IN-PROGRESS REVIEW AND STATE-OF-SCIENCE MEETING

The VRP held a Retina and Optic Nerve Injury Research In-Progress Review and State-of-Science meeting on January 31, 2022. More than 40 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 participated in the meeting, which showcased progress made in retina and optic nerve injury research and identified challenges remaining. Col. Marcus Colyer, M.D., a retinal specialist and Army Ophthalmology Consultant to the Surgeon General, gave an overview on the management of vitreoretinal injuries following combat ocular trauma. Five investigators presented their VRP-funded research aiming to develop therapies for a number of retina and optic nerve injury conditions. The speaker and attendees participated in an open panel discussion of ocular trauma models, approaches of therapeutic development, and considerations for clinical translation.

APPENDIX A: FY21-FY22

Table A-1. *CDMRP Programs, Appropriations, and Applications Received and Awarded in FY21-FY22*

Research Programs Managed by the CDMRP	FY21			FY22	
	Funds Received (in millions)	Applications Received	Applications Funded	Funds Received (in millions)	Applications Received to Date
Alcohol and Substance Use Disorders	$4	4	1	$4	0
Amyotrophic Lateral Sclerosis	$40	90	40	$40	74
Autism	$15	89	14	$15	80
Bone Marrow Failure	$7.5	47	10	$7.5	24
Breast Cancer	$150	1,297	87	$150	868
Breast Cancer Research Semipostal[1]	$0.5		2	$0.5	0
Chronic Pain Management	$15	105	13	$15	0
Combat Readiness Medical Research	$10	40	6	$10	51
Duchenne Muscular Dystrophy	$10	68	13	$10	0
Epilepsy	$12	38	15	$12	47
Gulf War Illness	$22	61	13	$0	0
Hearing Restoration	$10	36	9	$10	0
Joint Warfighter Medical[2]	$40	84	17	$40	61
Kidney Cancer	$50	184	56	$50	134
Lung Cancer	$20	380	38	$20	303
Lupus	$10	67	13	$10	40
Melanoma	$30	239	43	$40	76
Military Burn	$10	68	11	$10	0
Multiple Sclerosis	$20	118	23	$20	52
Neurofibromatosis	$20	71	20	$20	58
Orthotics and Prosthetics Outcomes	$15	34	10	$20	38
Ovarian Cancer	$35	258	52	$45	274
Pancreatic Cancer	$15	83	24	$15	32
Parkinson's	$16	72	16	$16	95
Peer Reviewed Alzheimer's	$15	59	15	$15	72
Peer Reviewed Cancer[3]	$115	579	87	$130	462
Peer Reviewed Medical[4]	$370	1,252	192	$370	1,288
Peer Reviewed Orthopaedic	$30	77	20	$30	95
Prostate Cancer	$110	471	112	$110	480
Rare Cancers	$17.5	226	44	$17.5	237
Reconstructive Transplant	$12	65	17	$12	0
Scleroderma	$5	39	11	$0	0
Spinal Cord Injury	$40	173	29	$40	259
Toxic Exposures				$30	0
Tick-Borne Disease	$7	44	8	$7	30
Traumatic Brain Injury and Psychological Health	$175	445	87	$175	208
Tuberous Sclerosis	$8	59	13	$8	43
Vision	$20	67	19	$20	0
Total	**$1,501**	**7,089**	**1,200**	**$1,545**	**5,481**

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

[2] Joint Warfighter Medical Execution Management Breakdown: 9 awards funded with 6.3 dollars, 2 awards funded with 6.4 dollars and 3 mods managed by CDMRP; 2 mods managed by the Navy and 1 mod managed by the Air Force.

[3] FY22 Peer Reviewed Cancer Research Program: The agreement provides $130.0M 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: bladder cancer, blood cancers, brain cancer, colorectal cancer, endometrial cancer, esophageal cancer, germ cell cancers, head and neck cancer, liver cancer, lymphoma, mesothelioma, metastatic cancers, myeloma, neuroblastoma, pediatric, adolescent, and young adult cancers, pediatric brain tumors, stomach cancer, sarcoma, thyroid cancer, and Von Hippel-Lindau syndrome malignancies (excluding cancers of the kidney and pancreas).

[4] FY22 Peer Reviewed Medical Research Program: The agreement provides $370.0M 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, cardiomyopathy, congenital heart disease, diabetes, dystonia, eating disorders, Ehlers-Danlos syndrome, endometriosis, epidermolysis bullosa, familial hypercholesterolemia, fibrous dysplasia, focal segmental glomerulosclerosis, food allergies, fragile x, Friedreich's ataxia, frontotemporal degeneration, Guillain-Barre syndrome, hemorrhage control, hepatitis b, hydrocephalus, hypercholesterolemia, hypertension, inflammatory bowel diseases, interstitial cystitis, malaria, mitochondrial disease, musculoskeletal disorders related to acute and chronic bone conditions and injuries, myalgic encephalomyelitis/chronic fatigue syndrome, myotonic dystrophy, nephrotic syndrome, non-opioid therapy for pain management, nutrition optimization, pancreatitis, pathogen-inactivated blood products, peripheral neuropathy, plant-based vaccine, platelet-like cell production, polycystic kidney disease, pressure ulcers, pulmonary fibrosis, respiratory health, Rett syndrome, rheumatoid arthritis, sleep disorders and restriction, suicide prevention, sustained release drug delivery, trauma, vascular malformations, viral diseases, and women's heart disease.

APPENDIX B: ACRONYMS

3D ..... Three-Dimensional
AA ..... African American
AD ..... Alzheimer's Disease
ADRD ..... Alzheimer's Disease-Related Dementias
AFHSB ..... Armed Forces Health Surveillance Branch
AIH ..... Acute Intermittent Hypoxia
AIM-CBCT for PTSD ..... Abbreviated, Intensive, Multi-Couple Group Format of Cognitive-Behavioral Conjoint Therapy for Post-Traumatic Stress Disorder
ALS ..... Amyotrophic Lateral Sclerosis
ALSRP ..... Alcohol and Substance Use Disorders Research Program
AoE ..... Areas of Emphasis
ARP ..... Autism Research Program
ASD ..... Autism Spectrum Disorder
ASUD ..... Alcohol Substance Use Disorders
ASUDRP ..... Alcohol Substance Use Disorders Research Program
BCRP ..... Breast Cancer Research Program
BET ..... Bromodomain and Extra-Terminal
BLBC ..... Basal-Like Breast Cancer
BMBC ..... Brain-Metastatic Breast Cancer
BMF ..... Bone Marrow Failure
BMFRP ..... Bone Marrow Failure Research Program
CA ..... Caucasian American
CAF ..... Cancer-Associated Fibroblast
CBCT ..... Cognitive-Behavioral Conjoint Therapy
CCCRP ..... Combat Casualty Care Research Program
CDC ..... Centers for Disease Control and Prevention
CDMRP ..... Congressionally Directed Medical Research Programs
CHD ..... Congenital Heart Defects
CMV ..... Cytomegalovirus
CNS ..... Central Nervous System
CPG ..... Clinical Practice Guidelines
CPMRP ..... Chronic Pain Management Research Program
CRRP ..... Combat Readiness – Medical Research Program
CTA ..... Clinical Trial Award
DBA ..... Diamond-Blackfan Anemia
DC ..... Dyskeratosis Congenita
DHP ..... Defense Health Program
DMD ..... Duchenne Muscular Dystrophy
DMDRP ..... Duchenne Muscular Dystrophy Research Program
DMSS ..... Defense Medical Surveillance System
DOD ..... Department of Defense
DSI ..... Decision Support Intervention
EC ..... Endothelial Cell
ECI ..... Early-Career Investigator
ER ..... Endoplasmic Reticulum
ERP ..... Epilepsy Research Program
FA ..... Fanconi Anemia
FDA ..... Food and Drug Administration
FPA ..... Focused Program Award
FTP ..... 18F-bnTP Probe
FY ..... Fiscal Year
Gd MRI ..... Gadolinium-Enhancing Metal Contrast Magnetic Resonance Imaging
GI ..... Gastrointestinal
GWAS ..... Genome Wide Association Studies
GWI ..... Gulf War Illness
GWIRP ..... Gulf War Illness Research Program
HAP ..... Hydroxyapatite
HDAC ..... Histone Deacetylases
HDL-C ..... High-Density Cholesterol
HEROIC ..... "Health Equity Research and Outcomes Health Equity Research and Outcomes Improvement Consortium"
HRRP ..... Hearing Restoration Research Program
HSC ..... Hematopoietic Stem Cells
IA ..... Idea Award
IDA ..... Idea Development Award
IDA-NICO ..... Idea Development Award – New Investigator Collaboration Option
IIRA ..... "Investigator-Initiated Research Award Investigator-Initiated Research Awards"
ILD ..... Interstitial Lung Disease
IND ..... Investigational New Drug
IPR ..... In-Progress Review
IQ ..... Intelligence Quotient
JPC ..... Joint Program Committees
JWMRP ..... Joint Warfighter Medical Research Program
KCRP ..... Kidney Cancer Research Program
LCRP ..... Lung Cancer Research Program
LEAP ..... Low-Force Expanding-Adaptable Pediatric
LH2 ..... Lysyl Hydroxylase 2
LRP ..... Lupus Research Program
M ..... Million
MASA ..... Melanoma Academy Scholar Award
MBRP ..... Military Burn Research Program

MCAA ..... Mid-Career Accelerator Award
MDS ..... Myelodysplastic Syndrome
MHS ..... Military Health System
MIDRIP ..... Military Infections Diseases Research Program
MMF ..... Mycophenolate Mofetil
MOMRP ..... Military Operational Medicine Research Program
MPNSTs ..... Malignant Peripheral Nerve Sheath Tumors
MRI ..... Magnetic Resonance Imaging
MRP ..... Melanoma Research Program
MRT ..... Malignant Rhabdoid Tumors
MS ..... Multiple Sclerosis
MSRP ..... Multiple Sclerosis Research Program
MST ..... Military Sexual Trauma
mTOR ..... Mammalian Target of Rapamycin
NETP ..... Neurotoxin Exposure Treatment Parkinson's
NF ..... Neurofibromatosis
NF1 ..... Neurofibromatosis Type 1
NF2 ..... Neurofibromatosis Type 2
NFRP ..... Neurofibromatosis Research Program
NIDCD ..... National Institute on Deafness and Other Communication Disorders
NIN ..... National Institutes of Health
NOD ..... New Onset Diabetes
NSCLC ..... Non-Small Cell Lung Cancer Treatment
OCRP ..... Ovarian Cancer Research Program
OUD ..... Opioid Use Disorder
PCa ..... Prostate Cancer
PCARP ..... Pancreatic Cancer Research Program
PCRP ..... Prostate Cancer Research Program
PDAC ..... Pancreatic Ductal Adenocarcinoma
PDX ..... Patient-Derived Xenograft Models
PET ..... Positron Emission Tomography
PFCs ..... Polyfluoroalkyl Chemicals
PI ..... Principal Investigator
PKD ..... Polycystic Kidney Disease
PLIE ..... Preventing Loss of Independence Through Exercise
PNH ..... Paroxysmal Nocturnal Hemoglobinuria
PRARP ..... Peer Reviewed Alzheimer's Research Program
PRCA ..... Pure Red Cell Aplasia
PrEP ..... Pre-Exposure Prophylaxis
PRMRP ..... Peer Reviewed Medical Research Program
PRORP ..... Peer Reviewed Orthopaedic Research Program
PSA ..... Prostate-Specific Antigen
PTE ..... Post-Traumatic Epilepsy
PTH ..... Post-Traumatic Headache
PTSD ..... Post-Traumatic Stress Disorder
R&D ..... Research and Development
RCRP ..... Rare Cancers Research Program
REBOA ..... Resuscitative Endovascular Balloon Occlusion of the Aorta
RFI ..... Request for Information
RMC ..... Renal Medullary Carcinoma
RRMS ..... Relapsing-Remitting Multiple Sclerosis
RTRP ..... Reconstructive Transplant Research Program
SBIR ..... Small Business Innovation Research
SCCOHT ..... Small Cell Carcinoma of the Ovary, Hypercalcemic Type
SCIRP ..... Spinal Cord Injury Research Program
SCLC ..... Small Cell Lung Cancer
SCN ..... Severe Congenital Neutropenia
SCS ..... Scientific Classification System
SCST ..... Sex Cord-Stromal Tumors
SHARC ..... Self-Sensing Hemorrhage Control and Resuscitative Catheter
SLE ..... Systemic Lupus Erythematosus
sNFL ..... Serum Neurofilament Light Chain
SOCOM ..... Special Operations Command
SRP ..... Scleroderma Research Program
SSc ..... Scleroderma/Systemic Sclerosis
STTR ..... Small Business Technology Transfer
SWAT ..... Short Wave Assessment Tool
TACE ..... TNFα-Converting Enzyme
TAM ..... Tumor-Associated Macrophage
TBD ..... Tick-Borne Disease
TBDRP ..... Tick-Borne Disease Research Program
TBI ..... Traumatic Brain Injury
TDA ..... Therapeutic Development Award
TERP ..... Toxic Exposures Research Program
TIA ..... Therapeutic Idea Award
TMEM ..... Tumor MicroEnvironment of Metastasis
TRA ..... Translational Research Awards
TRCC ..... Translocation Renal Cell Carcinoma
Tregs ..... Regulatory T Cells
TRPA ..... Translational Research Partnership Award
TSA ..... Team Science Award
TSC ..... Tuberous Sclerosis Complex
TSCRP ..... Peer Reviewed Tuberous Sclerosis Complex Research Program
USAMMDA ..U.S. Army Medical Materiel Development Activity
USAMRDC ..... U.S. Army Medical Research and Development Command
UV ..... Ultraviolet
VA ..... U.S. Department of Veterans Affairs
VBD ..... Vector-Borne Disease
VCA ..... Vascularized Composite Allotransplantation
VEGS ..... Virtual Environment Grocery Store
VRP ..... Vision Research Program

For more information, visit: https://cdmrp.health.mil/

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