US Army Medical Research and Development Command

CDMRP

Department of Defense

Congressionally Directed Medical Research Programs

2020 Annual Report

Letter from the Director

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

For the last 27 years, the Congressionally Directed Medical Research Programs (CDMRP) have focused our efforts on funding innovative and impactful research through important collaborations. We are grateful to our partners who are essential in helping CDMRP achieve our vision and we very much appreciate the support from Congress, consumer advocates, scientists, clinicians, professional organizations, academia, and military communities.

In an effort to remain transparent with the public and our stakeholders, I am pleased to present the 2020 CDMRP Annual Report. The intent of this report is to share research program information, funding profiles, the numbers and types of projects awarded, and specific highlights and outcomes for each our of programs. CDMRP currently has 34 research programs that are all aimed at making scientific breakthroughs in military medical research, cancer research, and other disease-, disorder-, and injury-specific research.

As the new Director of the CDMRP, I look forward to fostering continued collaborations, to identify and fund important medical research advances, and to help transform healthcare for our Service members, Veterans, and the American public.

Sincerely,
Sarah
Colonel Sarah B. Goldman, Ph.D.
Director, CDMRP
US 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, 2020

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INTRODUCTION

History and Overview

The Congressionally Directed Medical Research Programs (CDMRP) is a global funding organization that fosters novel approaches to biomedical research in response to the expressed needs of its stakeholders–the American public, the military, and Congress. CDMRP originated in 1992 when Congress first appropriated funds to the Department of Defense (DOD), specifically for breast cancer research. Since that time, Congress has added additional research programs and topics. CDMRP now manages individual research programs focused on military medical research, cancer research, and other disease-, disorder-, and injury-specific research. All the programs managed by CDMRP share the common goal of advancing paradigm-shifting research, solutions that will lead to cures or improvements in patient care, or breakthrough technologies and resources for clinical benefit. CDMRP strives to transform healthcare for Service members and the American public by funding innovative and impactful research. CDMRP oversees the investment of congressionally directed dollars to fund groundbreaking, high-impact, high-risk, high-reward, meritorious research that targets critical research gaps. CDMRP also provides management support of intramural and extramural military medical research.

CDMRP is located under the US Army Futures Command and within US Army Medical Research and Development Command (USAMRDC). Since it first originated in fiscal year 1992 (FY92), CDMRP has been responsible for managing more than $15.94 billion (B) in funding targeted for congressionally directed research areas/topics.

Fiscal Year 2020

CDMRP managed FY20 appropriations for 31 out of 32 existing programs and also for 3 additional new research programs: the Pancreatic Cancer Research Program (page 72), the Rare Cancers Research Program (page 86), and the Scleroderma Research Program (page 90). CDMRP managed funding over the last 10 years is displayed in **Figure 1**.

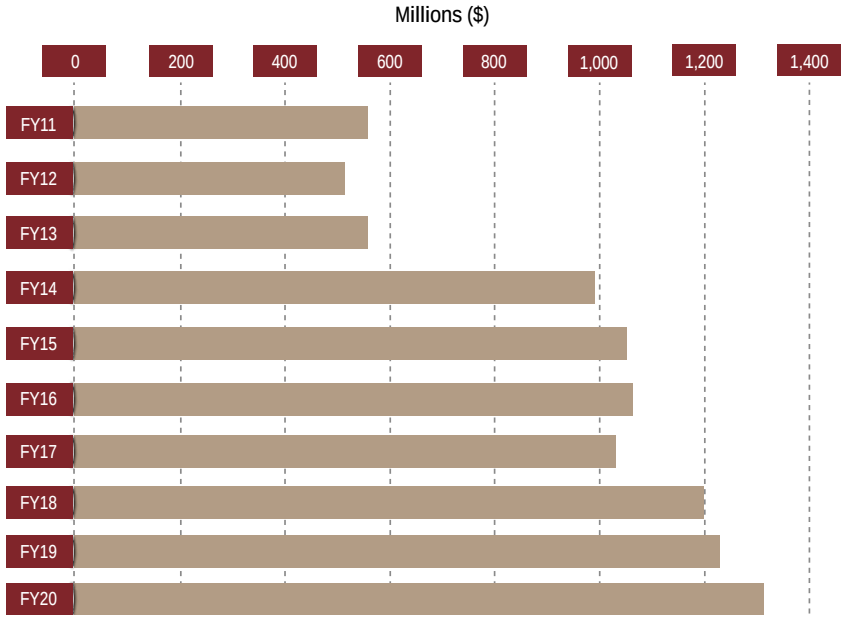

Figure 1. FY11–FY20 Research Funding

Vision: **Transform healthcare for Service members and the American public through innovative and impactful research**

Mission: **Responsibly manage collaborative research that discovers, develops, and delivers healthcare solutions for Service members, Veterans, and the American public**

Major Undertakings in FY20

Electronic Biomedical Research Application Portal and the Electronic Grants System

The Electronic Biomedical Research Application Portal (eBRAP) and Electronic Grants System (EGS) are Defense Business Certified systems that provide USAMRDC and DOD unique mission-critical capabilities not available in other systems for processing and management of both intramural and extramural DOD biomedical research applications and awards. The eBRAP/EGS solution was selected in FY18 as the Military Health System Grants Administration system through an 18-month process of evaluation and cost benefit analysis. Use of eBRAP/EGS is being expanded to other DOD user groups to realize efficacies, streamline processes, and increase transparency of biomedical research across the enterprise.

eBRAP is an Extramural and Intramural research pre-application and full application receipt, processing, and management portal that supports the missions of the Defense Health Agency (DHA), USAMRDC, the US Army Medical Research Acquisition Activity (USAMRAA), the Special Operations Command, and CDMRP. In response to 140 FY19 funding opportunities, eBRAP received and processed over 9,000 pre-applications and over 5,800 full applications. During FY20, eBRAP is managing about 130 funding opportunities, with pre-application and full application receipts extending from December 2019 through December 2020.

eBRAP Highlights:

- Streamlines operational efficiency and effectiveness in retrieving and processing applications from grants.gov.
- Provides worldwide web-based accessibility in over 110 countries for receipt and processing of pre-applications, full applications, and documents required throughout the life cycle of an award.
- Supports business process to fund biomedical research that meets congressional and DOD missions by providing nimble responsiveness to annual changes in appropriations, congressional language, and program focus.
- Has multi-user functionality allowing eBRAP to be easily customized via "plug and play" components to accommodate the varying needs of each organization, research program, and each Program Announcement.
- Provides functionality to the military medical community by directly accepting DOD intramural application submissions, which is not supported by Grants.gov.
- Provides capability to communicate with the research community both on a one-to-one basis and in batches and uses milestone-triggered automated delivery of communications to the research community.
- Provides real-time customer service to answer researchers' questions and manage the pre-application and application components required for award execution.
- Supports data transfer to EGS and other systems.

EGS is the back-end business system that focuses on activities related to management of funded awards from award negotiations to closeout, regulatory reviews, and program evaluation. The system allows multiple organizations to collaborate in a virtual workspace to facilitate communication between user groups, serving as the central repository of research administration data and conduit of information for other systems.

EGS Highlights:

- EGS enables real-time comprehensive electronic workflows among USAMRDC Program Offices, USAMRAA, the Office of Surety, Safety and Environment, and the Office of Research Protections (ORP), which can manage the complete life cycle of animal and human research.
- Multiple user groups are able to collaborate online, enabling data input, the generation of reports, research award management, and the categorization of research outputs in customized modules to allow for data mining, analysis, and reporting to stakeholders.
- System-to-system interfaces allow transfer of data between DOD agencies, as well as data transfers to external systems, including the International Cancer Research Partnership, National Institutes of Health (NIH) Query View Report, and Federal RePORTER.
- Award data in EGS, including abstracts and publications, are automatically made public nightly via the CDMRP website, allowing for real-time transparency with CDMRP stakeholders.
- Use of EGS has expanded to include management of DOD Intramural awards by several Joint Program Committees (JPCs)/Program Area Directorates (PADs) and other USAMRDC organizations.

Interagency Data Sharing

In response to US Government Accountability Office recommendations (GAO-12-342SP) to address duplication of research efforts across federal funding agencies, the CDMRP entered into a Memorandum of Agreement (MOA) with the NIH to share pre-award application information to allow for greater visibility in decision-making processes. After completing a feasibility study and pilot program, starting in 2019, the agencies began sharing data shared between its two research administration systems, Electronic Research Administration (eRA) at the NIH and EGS at CDMRP. By consolidating data in the eRA database and making it available through the Query View Report module, scientific staff are now able to view real-time data on incoming research applications and current funding statuses as well as utilize a unique fingerprinting technology to assist in identification of duplicate and overlapping projects. Within the first year of use, the CDMRP was able to streamline and efficiently process applications during the awarding phase while eliminating duplication where possible. This data-sharing initiative has the potential to further increase collaboration and increase efficiencies as additional capabilities are being explored.

Our Programs

Highlights of FY19–FY20 programs managed and/or supported by CDMRP can be found within the program pages in this Annual Report, beginning on page 25. As detailed in **Table 1**, CDMRP successfully obligated FY19 appropriations across 33 programs, encompassing 923 research awards. In addition, in FY20, CDMRP initiated the management of over $1.31B across 35 programs.

"The autism clinical trials program in the CDMRP serves a critical role. The basic and translational science underlying the neurobiology of autism spectrum disorder (ASD) is generally supported by NIH. Some of these discoveries lead to trials pursued within the pharmaceutical industry. However, many important discoveries exist in the space of repurposed drugs or other treatments that would not be patentable, and therefore would not be pursued by the pharmaceutical industry. It is the CDMRP that has played a key role in bringing these discoveries to the potential reality of clinical benefit."

David Beversdorf, M.D., University of Missouri

Table 1. CDMRP Programs, Appropriations, and Applications Received and Awarded in FY19-FY20

Research Programs Managed by the CDMRP	FY19				FY20	
	Funds Received (in millions)	Applications Received	Applications Funded	Funding **Modifications** Completed[1]	Funds Received (in millions)	Applications Received to Date
Alcohol and Substance Abuse Disorders	$4.0	0	0	3	$0.0	
Amyotrophic Lateral Sclerosis	$10.0	55	11	0	$20.0	87
Autism	$7.5	59	8	0	$15.0	96
Bone Marrow Failure	$3.0	27	6	0	$3.0	26
Breast Cancer	$130.0	1,459	96	2	$150.0	1,505
Breast Cancer Research Semipostal[2]	$0.6	0	0	2	$0.5	
Chronic Pain Management	$10.0	54	7	0	$15.0	
Combat Readiness Medical Research	$15.0	170	8	0	$10.0	
Duchenne Muscular Dystrophy	$3.2	23	5	1	$10.0	
Epilepsy	$7.5	29	7	1	$12.0	44
Gulf War Illness	$22.0	53	12	2	$22.0	40
Hearing Restoration	$10.0	39	10	1	$10.0	
Joint Warfighter Medical[3]	$50.0	56	7	3	$40.0	48
Kidney Cancer	$20.0	205	33	0	$40.0	232
Lung Cancer	$14.0	349	31	0	$14.0	359
Lupus	$5.0	117	13	1	$10.0	69
Melanoma	$10.0	187	19	0	$20.0	186
Military Burn	$8.0	57	13	0	$10.0	17
Multiple Sclerosis	$6.0	65	11	0	$16.0	97
Neurofibromatosis	$15.0	61	21	1	$15.0	86
Orthotics and Prosthetics Outcomes	$10.0	34	10	1	$15.0	54
Ovarian Cancer	$20.0	180	25	1	$35.0	233
Pancreatic Cancer[4]	n/a	n/a	n/a	n/a	$6.0	
Neurotoxin Exposure Treatment Parkinson's	$16.0	105	16	0	$16.0	76
Peer Reviewed Alzheimer's	$15.0	54	17	0	$15.0	55
Peer Reviewed Cancer	$90.0	673	120	0	$110.0	622
Peer Reviewed Medical	$350.0	1,405	224	9	$360.0	1,940
Peer Reviewed Orthopaedic	$30.0	67	21	2	$30.0	92
Prostate Cancer	$100.0	500	93	3	$110.0	570
Rare Cancers[4]	n/a	n/a	n/a	n/a	$7.5	
Reconstructive Transplant	$12.0	66	20	0	$12.0	
Scleroderma[4]	n/a	n/a	n/a	n/a	$5.0	
Spinal Cord Injury	$30.0	128	19	3	$40.0	152
Tick-Borne Disease	$5.0	63	8	1	$7.0	39
Tuberous Sclerosis	$6.0	47	10	0	$6.0	44
Vision	$20.0	68	22	0	$20.0	
Additional Supported DOD Programs/Projects						
Armed Forces Institute of Regenerative Medicine II	$7.7	0	0	14		
Defense Medical Research and Development[5]	$99.0	346	41	24	$60.1	
Defense Medical Research and Development Congressional Special Interest Restoral[6]	$49.4	0	30	4	$60.6	
Psychological Health/Traumatic Brain Injury	$59.9	81	26	23	$56.8	
Small Business Innovation Research/ Small Business Technology Transfer	$34.1	40	38	3	$1.6	26
Trauma Clinical	$10.0		0	0	$10.0	
Other Submission Processes						
USAMRDC - Broad Agency Announcement[7]		71				8
Total	$1,314.9	6,993	1,058	105	$1,416.1	6,803

[1] Funding Modifications Completed are incremental and option year funding provided for prior year awards.
[2] Breast Cancer Semipostal funds applications received and reviewed by the Breast Cancer Research Program
[3] Joint Warfighter Medical Execution Management Breakdown: 7 awards and 2 modifications managed by CDMRP; 0 awards and 0 modifications managed by USAMMDA; and 0 modifications managed by USAMMA
[4] New in FY20
[5] Includes 2013-2015 Clinical Research Intramural Initiative and 2010 Chiropractic Clinical Trials.
[6] Includes 2016-2019 Clinical Research Intramural Initiative.
[7] CDMRP manages the application receipt and review process for the USAMRMC Broad Agency Announcement. Funded proposals that are managed by CDMRP counted in the program that provided the funding. Of the 71 applications received, CDMRP funded 13.

OUR MANAGEMENT CYCLE

Under the leadership of a CDMRP Program Manager, each program follows the management cycle described in detail on the following pages. **Figure 2** depicts each step in the management cycle, and each step is further described below.

Funding Process

The DOD sends a budget request to Congress in the form of the President's Budget; however, CDMRP funding is not considered part of the DOD's core mission and is therefore not included in the DOD's requested budget. Rather, congress has added funding for CDMRP to execute research programs in the annual Defense Appropriations Bill since FY92. The annual congressional legislation known as the Defense Appropriations Act, details funding for the CDMRP.

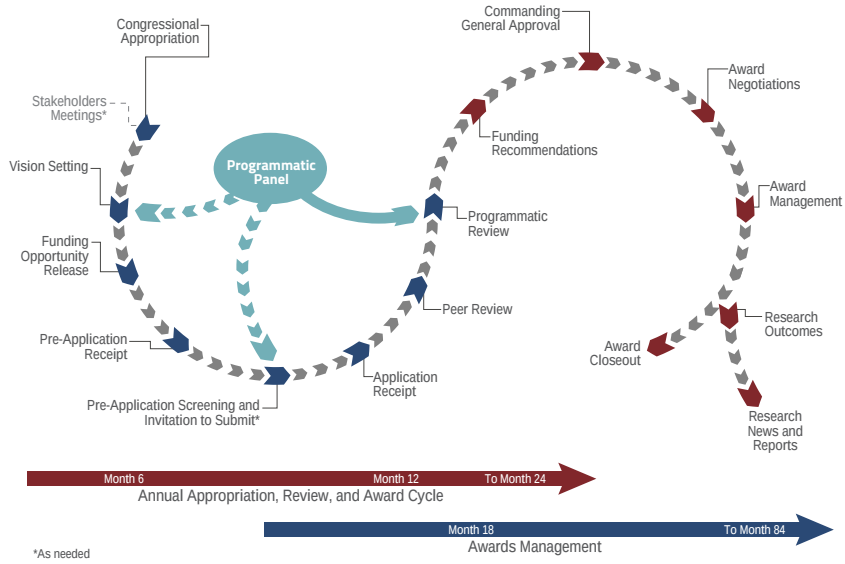

Figure 2. CDMRP Management Cycle

Steps in the CDMRP Management Cycle

1	**Congressional Appropriation, Core Dollars, and Receipt of Funds** Annually, funds for CDMRP programs are added to the Defense Appropriations Bill in response to the needs of Service members, beneficiaries, research communities, consumers, and the public at large.
2	**Stakeholders Meeting** A Stakeholders meeting is held at the initiation of a new program and periodically thereafter. The meeting brings together stakeholders to survey the research landscape in order to identify important gaps and opportunities for research. Stakeholders are world-renowned consumers, scientists, clinicians, and other funders who have an interest in any given field or topic related to the program. The recommendations developed at the Stakeholders meeting are used to inform vision setting.

CDMRP has developed a best-practices-based flexible management cycle that is responsive to the needs of both the individual programs and the requirements of the stakeholders for each program, including Congress, the DOD, researchers, consumer communities, and the American public.

3 Vision Setting

The purpose of an annual Vision Setting meeting is to discuss the current landscape of the disease, condition, or injury; identify scientific and clinical research gaps; assess the program portfolio and develop a recommended investment strategy to fill the identified gaps. The process of vision setting brings together a Programmatic Panel of experts in science, the clinic, the military, and consumers to determine the program's goals and recommend award mechanisms. Based on the recommendations of the National Academy of Medicine, the vision-setting process concludes with the development of an annual investment strategy for the program's available funds. Funding opportunities are developed to support the gaps and goals identified by the panel of scientific experts and consumers for the program year. To ensure impartiality and the integrity of the process, Programmatic Panel members are prohibited from applying for funds for the fiscal year in which they participate in vision setting.

4 Program Announcements and Broad Agency Announcements

The award mechanisms are released as PAs or Broad Agency Announcements (BAAs), depending on the goals of the program. Both of these solicitations provide applicants with details about a particular funding opportunity. Components of these announcements include: the programmatic intent, a description of the type of studies being requested, eligibility, and submission requirements, including the application review criteria and processes.

5 Applicant Submission and Receipt

For all of the award mechanisms, application submission requires a multistep process consisting of pre-application submission (which includes a letter of intent or a pre-proposal as specified in the PA or BAA), followed by full application submission. Pre-proposals may be screened by either the Programmatic Panel or other recruited experts, based on the requirements described in each PA or BAA. The final product of the pre-proposal screening is a list of invited applicants. In FY20, CDMRP received 6,317 pre-proposals that, after screening and invitation, resulted in 3,080 full applications received. In addition, CDMRP received 5,608 full applications from mechanisms that required a letter of intent, for a total of 8,688 full applications received in this fiscal year. The number of submissions are summarized in **Table 2**.

On October 1, 2014, CDMRP began oversight of the receipt and review of submissions to the USAMRDC BAA for Extramural Medical Research, a funding opportunity that is open year-round and solicits projects aligned to research areas and topics of interest to USAMRDC and the DHA. These areas of interest are determined annually by the USAMRDC PADs/JPCs in response to evolving research priorities and knowledge gaps. For FY20, 15 pre-applications and 8 full applications were submitted to the BAA process and forwarded to the USAMRDC PADs/JPCs for programmatic decisions.

Table 2. Number of Submissions Received October 1, 2019 - September 30, 2020, across FY19-FY20 Programs

Pre-Application Submissions	
Pre-proposals screened	6,371
Letters of intent received	6,915
Total pre-applications received	13,286
Full Application Submissions	
Full applications from invitations only	3,080
Full applications from letters of intent	5,608
Total full applications	8,688

Multistep Process to Minimize Award Duplication and Overlap

Step 1	Step 2	Step 3	Step 4	Step 5	Step 6	Step 7
Principal Investigators (PIs) are required to submit a list of past, current, and pending funding support at the time of application submission.	Screen for duplicate submissions during compliance checks.	Identification of project innovation, research duplication, and overlap during the two-tier review process by peers in the field (specifically program staff from other federal funding agencies).	List of updated funding support at the time of award notification, which is certified by the award recipient's Sponsored Programs Office.	Review of submitted documents and research program sites to assess pending and existing funding support during award negotiations.	PIs are required to provide a list of updated funding support in annual technical progress reports.	Technical review of progress and review of Federal RePORTER and other research funding entities annually throughout the award period of performance, which includes a review for funding overlap and duplication.

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Two-Tier Review Process

The two-tier review process of applications includes both peer review and programmatic review and is based on the recommendations set forth by the Institute of Medicine (IOM) committee in 1993 and affirmed in the 2016 report. CDMRP's goal is to give every application a fair and balanced review. Steps are taken to ensure that conflicts of interest do not influence the process and that the needs of the Warfighter and their beneficiaries are taken into account. Additional details regarding the two tiers of review can be accessed on the CDMRP website at https://cdmrp.army.mil/about/2tierRevProcess.

Peer Review: Peer review is a criteria-based process in which discipline-specific panels assess applications for scientific and technical merit. The peer review panel evaluates each application based on the review criteria outlined in the PA or BAA. Although some peer review panel members may participate in similar panels annually, peer review does not convene a standing panel. Rather, CDMRP tailors the review panels to fit the specific expertise required by the research program, award mechanism, and applications received. During peer review, each application is evaluated for its own scientific and technical merit, independent of other applications. The product of peer review is a summary statement that describes the strengths and weaknesses of the application in accordance with the published review criteria and includes an overall peer review score. Summary statements serve as the basis for the second tier of review, Programmatic Review.

Programmatic Review: After applications have been peer reviewed, they go through programmatic review, a comparison-based process in which applications of high scientific and technical merit compete in a common pool. Programmatic review is conducted by a Programmatic Panel comprised of renowned experts, including scientists, clinicians, military members, and/or consumers. Names and affiliations of Programmatic Panel members for each program are posted publicly on CDMRP's website each year prior to funding opportunity announcement release. At the programmatic review level, the Programmatic Panel uses the criteria published in the PA or BAA (e.g., programmatic relevance, relative innovation, portfolio balance, military impact, portfolio balance, adherence to the intent of the mechanism, and scientific merit) in a comparison-based assessment of submitted applications. Although the ratings and evaluations of the peer reviewers are a key factor taken into consideration at programmatic review, applications that have the highest potential to help achieve the vision, mission, and goals of the respective program are recommended for funding. The product of programmatic review is a list of applications recommended for funding.

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Approval of the Funding Recommendations

The approval authority for all CDMRP applications is the Commanding General, USAMRDC, on behalf of the DHA J9, Research and Development Directorate and the Office of the Assistant Secretary of Defense for Health Affairs (OASD[HA]). Upon approval, electronic notification is sent to all program applicants to inform them of their funding status.

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Award Negotiations and Management

Negotiation and management of awards are a major focus of USAMRDC offices and organizations, including CDMRP, USAMRAA, and ORP. CDMRP actively manages and monitors award progress during the period of performance (which can vary according to award type and may include extensions). The awards management process is depicted in **Figure 3**. Over the past 5 years, an average of 950 new awards were made each fiscal year. As of September 30, 2020, CDMRP has managed 18,663 awards throughout its funding history.

Once an application has been recommended and approved for funding, it is assigned a CDMRP Science Officer, who serves as the technical representative and primary point of contact for the PI for the lifetime of the award. The Science Officer plays a key role in the partnership between the awardees institution, the PI, CDMRP, and offices within USAMRDC. In order to maximize savings and avoid overlap in research funding with other Federally funded projects, a technical analysis of the budget with respect to the scope of work to be performed is completed prior to the award being made. Once all aspects of negotiation are complete, an award is signed, and an assistance agreement (grant or cooperative agreement) is issued, a CDMRP Grants Officer's Representative is assigned to each

8 cont.

respective award and serves as the technical point of contact for the Grants Officer. The life-cycle management of awards continues throughout the period of performance, which can also include extension periods. Aspects of award management include monitoring of the technical progress and research outcomes through annual/quarterly reports, animal and human subject's protections review (as relevant), financial reporting, and avoiding funding duplication. Throughout the period of performance CDMRP, works with the PI and other DOD components to provide active management, facilitate communication, promote successful completion of awards, and accelerate translation of research outcomes where possible.

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Award Closeout

Award closeout takes place at both USAMRAA and CDMRP and is usually performed within 6 months after the period of performance has expired. During this time, CDMRP carefully reviews the final progress report and the patent report, while USAMRAA reviews the final financial accounting. Actions regarding any patents, invention disclosures, publications, and follow-up funding are captured during award closeout. When significant discoveries are identified, the awards are flagged for further follow-up, and the data is captured in CDMRP's EGS. In addition, PIs will be asked to complete an Award Expiration Transition Plan, which will outline if and how the research supported by the CDMRP award will transition to the next stage, including source(s) of funding, either known or pending.

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Research News and Reports/Public Relations

To maintain transparency, various communication processes and social media techniques are used to share information with stakeholders and the general public. The CDMRP website (https://cdmrp.army.mil) remains a central mode of communication to the public, featuring videos, news releases, research highlights, consumer stories, program books, annual reports, program strategic plans, and abstracts and publications for all awards. Information on the progress of awards can be found on the Defense Technical Information Center website at https://discover.dtic.mil/. Also included on the CDMRP website is a webinar series describing the types of funding opportunities offered and strategies to increase the success of applications submitted to different CDMRP programs. This has been a successful communication tool and will remain posted on the CDMRP website and be updated when new types of funding opportunities are offered. Social media outlets used by CDMRP to expand information dissemination strategies include Facebook (https://www.facebook.com/TheCDMRP) Twitter (https://twitter.com/CDMRP), and YouTube (https://www.youtube.com/user/CDMRP); in addition, CDMRP maintains an e-mail listserve of more than 50,000 unique recipients.

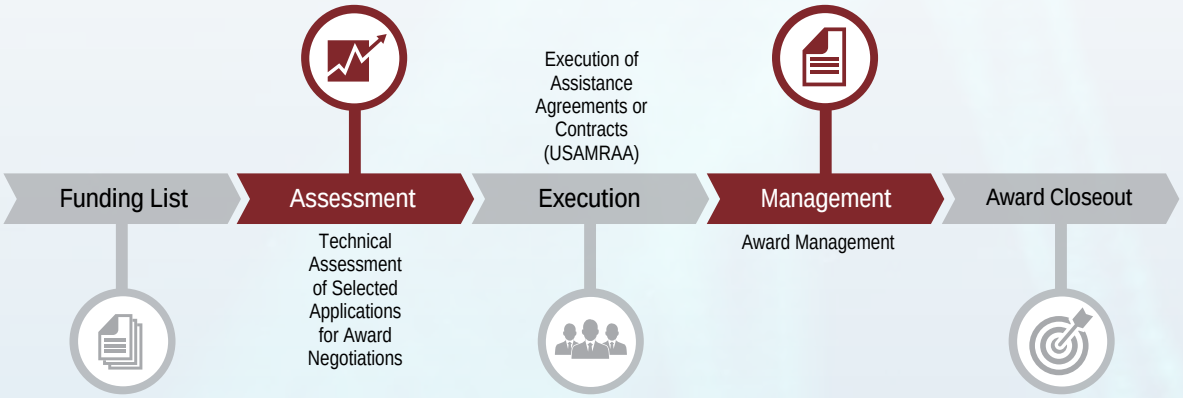


Figure 3. Awards Management Process

VITAL PARTNERSHIPS

Throughout the years, CDMRP fostered essential partnerships that enable it to fund innovative and impactful research areas and gaps as well as to prevent redundancy within each program's portfolio and across federal agencies. These include partnerships with the consumer and scientific communities, professional organizations, and military communities. The following sections discuss these partnerships and collaborations with stakeholders and other federal and non-federal agencies.

Consumers

A hallmark of CDMRP is the inclusion of consumers (patients, survivors, family members, and/or caregivers) in the review of research applications as full voting members. Consumers use their experiences to offer fresh, new perspectives and insights that other panel members may not have, and they bring a sense of urgency to the discussions. Consumers first served as reviewers for CDMRP at the programmatic review level in 1993, and their role soon expanded to scientific peer review in 1995. CDMRP developed a model of consumer inclusion that has been adopted by other funding agencies. Consumers are identified for review panels through nominations submitted by advocacy organizations. In each tier of review, consumers serve alongside scientists, clinicians, and leading experts and have an equal voice and vote in deliberations.

In 2020, nearly 466 consumers served on CDMRP peer review panels and over 73 served on programmatic panels. In addition, in 2020, 11 consumers served as ad hoc reviewers on CDMRP programmatic panels. Since inception in 1992, a total of 3,236 consumers have represented their communities and organizations at least once.

Throughout the growth of CDMRP, consumers and stakeholders remain the foundation for many of the programs executed and managed by CDMRP. For more information on consumer involvement, see the consumer involvement pages on the CDMRP website (http://cdmrp.army.mil).

The Scientific Community

The scientific community has been an essential partner in assisting CDMRP to shape the future of healthcare. Scientists and clinicians serve on both the peer and programmatic review panels during the review of applications; conduct the research that elucidates the complex causes of diseases, conditions, and injuries; and help translate this knowledge into improved prevention, treatment interventions, patient survival, and quality of life. External experts bring the most current and up-to-date knowledge to the table when they identify research strategies and field gaps during vision setting and when applications are being peer and programmatically reviewed.

In 2020, nearly 3,164 scientists and clinicians provided necessary subject matter expertise on peer review panels, and over 419 scientists and clinicians served on programmatic panels. In 2020, over 197 scientists and clinicians served as ad hocs on CDMRP programmatic panels.

Since inception, CDMRP has funded approximately 13,263 researchers to improve the health and quality of life of all people.

"I have participated in the CDMRP Ovarian Cancer Research Program (OCRP) for the past 3 years on the peer review panel. I am honored to participate in this program. I enjoy the consumer advocate program and love how the survivors are respected. We definitely feel like an important part of the team. I feel that the work done through OCRP is amazing and crucial to getting better treatment and ultimately curing ovarian cancer. The dedication I have seen in the researchers and clinicians is inspiring."

Lori Clemens, OCRP Consumer Reviewer

Military Partnerships

US Army Medical Research and Development Command

Vision: Lead the advancement of military medicine

Mission: Responsively and responsibly create, develop, acquire and deliver capabilities for the Warfighter

CDMRP is located within USAMRDC, the largest medical research enterprise within the DOD and the only organization solely focused on research and development (R&D) to address the military's unique medical requirements. USAMRDC supports six medical research laboratory commands that perform core science and technology research to develop medical solutions for the battlefield and beyond. USAMRDC focuses on medical research, development, and acquisition management to ensure the health and readiness of the US military's most important asset: the Warfighter.

Figure 4. The USAMRDC Team

CDMRP works in close partnership with key USAMRDC components, shown in **Figure 4**, to responsibly and efficiently manage appropriations according to congressional direction and provide active oversight of funded research awards to maximize benefit to Service members and the American public. Although all are important, two of the most critical CDMRP partners within USAMRDC include USAMRAA (release funding opportunities; negotiate and administer awards) and Office of Research Protections (review and approve animal and human use protocols).

CDMRP also coordinates with USAMRDC's medical materiel product developers at USAMMDA to leverage their expertise in helping shape program strategies and facilitate transition of products that address Warfighter needs.

Defense Health Agency J9, Research and Development Directorate

Vision: Bridging the future of military health and readiness

Mission: J-9 leads the discovery, development, and delivery of enhanced pathways to military health and readiness

The DHA is a joint, integrated Combat Support Agency that leads the Military Health System to deliver increased readiness, better health, better care, and lower cost. The DHA reports to OASD(HA). The DHA enables the Army, Navy, and Air Force medical services to provide both a medically ready force and ready medical force to Combatant Commands in both peacetime and wartime.

The DHA J9, Research and Development Directorate, was established within DHA in 2014 to help coordinate and enhance the related medical research and development programs of the Army, Navy, Air Force, and Defense Advanced Research Projects Agency. As directed by OASD(HA), the DHA J9, Research and Development Directorate, manages and executes the Defense Health Program (DHP) Research, Development, Test, and Evaluation (RDT&E) appropriation, providing centralized oversight of research and development across the Services and Military Health System to eliminate redundancy and reduce variance.

The DHA J9, Research and Development Directorate organizes annual focused Review and Analysis (R&A) meetings to facilitate short- and long-term planning of research within and across core medical R&D portfolios. These R&A meetings bring together senior leadership from across different military and government agencies (DOD, US Department of Veterans Affairs [VA], NIH, and US Department of Health and Human Services [HHS]) to give them visibility of the research, help identify program needs and issues, provide a forum for feedback and guidance, and identify possible sources of collaboration and cooperation. CDMRP-assigned congressional programs presented at R&A meetings in FY20. Participants highlighted research gaps being addressed by current programs, identified gaps requiring additional support, highlighted current areas of collaborative success, and also identified additional opportunities for further collaboration and coordination, leveraging resources, and avoiding overlap.

Joint Program Committees

The JPCs are DHA J9, Research and Development Directorate advisory bodies composed of DOD and non-DOD medical and military technical experts that provide guidance on funding recommendations and program management support for DHA J9, Research and Development Directorate-funded research. JPCs advise and work through the USAMRDC PADs, which provide strategic oversight of this research. In FY20, there were five active PADs:

- Medical Simulation and Information Sciences Research Program
- Military Infectious Diseases Research Program
- Military Operational Medicine Research Program
- Combat Casualty Care Research Program
- Radiation Health Effects Research Program

CDMRP provides award and program management support as requested to the JPCs/PADs for DHP core research program areas. The combined effort leverages CDMRP's expertise in research program administration with the PADs' technical and strategic expertise to expedite the delivery of products and solutions for the advancement of the DHA mission. CDMRP administers these programs as the Defense Medical Research and Development Program (DMRDP). DMRDP focuses on advancing the state of medical science as it relates to conditions directly relevant to battlefield injuries and other ailments that affect both Service members and beneficiaries. (For additional information about DMRDP and other programs/projects supported by CDMRP, see pages 104-107 in this report). In FY20, CDMRP assisted with program and award management in a number of areas relevant to battlefield injury and military Service, including psychological health and resilience, physiological health, neurotrauma, hemorrhage and resuscitation, en route and forward surgical care, medical simulation and training, wound infections, infectious diseases, prosthetics, vision, hearing, balance, pain, and other rehabilitative and regenerative medicine efforts. This partnership supports CDMRP's vision of transforming healthcare for Service members and the American public through innovative and impactful research.

US Department of Veterans Affairs

Many CDMRP programs focus on topics that are relevant to Veterans healthcare, and several align closely with areas of VA research. CDMRP and VA program staffs communicate and actively coordinate on related areas of program research to identify gaps, leverage funding, and prevent duplication of effort. Both Veterans and VA investigators serve as reviewers on CDMRP peer and programmatic review panels, and CDMRP funds VA investigators for both individual and collaborative research efforts. To date, more than 242 investigators at VA institutions have been funded by CDMRP.

One leading example is the CDMRP's Gulf War Illness Research Program's (GWIRP) collaboration with the VA to make the best possible use of available resources in support of high-quality, Veteran-focused research on Gulf War Illness (GWI) (see pages 46-47 for additional details on GWIRP). The GWIRP peer and programmatic review panels have VA scientists and clinicians that inform and help make funding recommendations. They also provide valuable resources and expertise as investigators on many GWIRP-funded awards. In another groundbreaking collaborative effort, the DOD and VA have combined more than $45 million (M) to fund two consortia aimed at improving diagnosis and treatment of mild traumatic brain injury (mTBI) and post-traumatic stress disorder (PTSD). These consortia include the Consortium to Alleviate Post-Traumatic Stress Disorder (refer to page 15) and the Long-Term Impact of Military-Relevant Brain Injury Consortium (refer to page 16), which are described in further detail on pages 13-22 of this Annual Report.

Additionally, in 2019 and 2020, the VA was invited to serve on the senior leadership and present VA-funded research efforts during the DHA-led R&As of CDMRP's programs.

COLLABORATIVE RESEARCH

CDMRP is leading the development and management of research consortia and/or initiatives to build strong partnerships and collaborations within the scientific community. These multi-institutional efforts serve the scientific community by addressing overarching issues in biomedical research, combining and sharing their resources, and fostering real-time communication and research results. Highlights of consortia and initiatives are provided in the following sections.

Alzheimer's Disease Neuroimaging Initiative

ADNI
Results from these studies will enable researchers to understand the complex relationships between TBI/PTSD and AD or a related dementia in Vietnam-era Veterans.

The DOD's Alzheimer's Disease Neuroimaging Initiative (ADNI) (http://www.adni-info.org/DOD.html) examines how both traumatic brain injury (TBI) and PTSD function as risk factors for Alzheimer's disease (AD) or a related dementia in Veterans as they age. TBI and PTSD are common combat-related problems subsequent to military Service. Both are putatively associated with a greater risk of developing AD or a related dementia. DOD ADNI is comprised of 19 study centers. All use standardized study protocols for all diagnostic, cognitive, and behavioral testing. The work here will quantitate cognitive and psychological changes in cohorts of Vietnam-era veterans with TBI, PTSD, and TBI/PTSD. Veterans participating in the cohort also agree to participate in imaging (positron emission tomography and magnetic resonance imaging) and biomarker (cerebrospinal fluid) research. Three studies totaling approximately $18M led by Dr. Michael Weiner at Northern California Institute for Research and Education comprise the DOD ADNI projects. The first study examines individuals with normal cognition with TBI and/or PTSD, while the second study examines individuals manifesting signs of mild cognitive impairment (memory disorders) in conjunction with TBI and/or PTSD. The third study evaluates state of the art nuclear imaging in these Veteran cohorts for its ability to detect tauopathies. All three studies were fully funded by the Peer Reviewed Alzheimer's Research Program.

Armed Forces Institute of Regenerative Medicine

AFIRM
The AFIRM is dedicated to repairing battlefield injuries through the use of regenerative medicine.

The Armed Forces Institute of Regenerative Medicine (AFIRM) was established in March 2008 by USAMRDC in partnership with the Office of Naval Research, US Air Force Office of the Surgeon General, NIH, Veterans Health Administration of the VA, and DHP. With funding totaling approximately $350M awarded to two separate consortia, these interdisciplinary networks were focused on regenerative medicine for the treatment of severely wounded Service members. Before ending in September 2018, the AFIRM supported nine clinical trials, resulting in the treatment of more than 200 patients with novel therapeutic strategies in wound repair and tissue replacement. In 2013, based on the AFIRM's successes, $75M was made available for the AFIRM II by many of the same government agencies. Led by Wake Forest, AFIRM II members include new investigators as well as many from the initial AFIRM consortia. Sixty research projects were launched addressing critical clinical challenges for Wounded Warriors across five Focus Areas: (1) composite tissue allotransplantation and immunomodulation; (2) craniomaxillofacial reconstruction; (3) extremity repair; (4) genitourinary repair and lower abdomen reconstruction; and (5) skin regeneration. Each Focus Area addresses restoring and regenerating tissue at

"My early research, funded by Tuberous Sclerosis Complex Research Program (TSCRP), led to discovery of a novel mechanism deregulated in tuberous sclerosis associated lymphangioleiomyomatosis (TSC-LAM) and paved the way toward a clinical trial. I am honored and delighted to serve on the TSCRP Programmatic Panel together with distinct experts in the field and representatives from TSC patients' families. Each year TSCRP advances high-impact research and brings us closer toward finding a cure for TSC."
Vera Krymskaya, Ph.D., University of Pennsylvania, Perelman School of Medicine, Programmatic Panel Member

the component and/or complex integrated structure levels (i.e., multiple tissues such as muscle, bone, nerve, skin, and vasculature as a functional unit, such as the face or hand), with the goal of not only improving the form and cosmetic appearance of traumatically injured sites, but also providing full functional recovery to the tissues affected by trauma. Regenerative medicine treatments include pharmacological and cell-based therapies that promote the self-regenerative capacity of the body, as well as implantable engineered constructs for the reconstruction of damaged tissue. Novel strategies being advanced include three-dimensional (3D) printing of tissues, in vivo bioreactors, bioactive protein implants with gradients, development of degradable implanted catheters to augment perfusion, wound infection treatment, and the concurrent regeneration of multiple tissue types. These materials and strategies follow the usual pathway of testing in small and large animal models and regulatory scrutiny followed by clinical trials in humans to test safety and efficacy. These projects include four completed clinical trials, six ongoing clinical trials, and two clinical trials awaiting final clearance from the US Food and Drug Administration (FDA) to proceed. A total of 73 products are being advanced, and these efforts have resulted in several spin-off companies for advanced development and commercialization.

Breast Cancer Prevention in High-Risk BRCA1 Mutation Carriers

BRCA-P Prevention trial
The goal of the clinical trial is to determine if RANK ligand inhibition with denosumab can prevent breast cancer in women with the BRCA1 gene mutation.

The BRCA-P Prevention trial, led by Drs. Judy Garber and Christian Singer, is an international Phase III clinical trial co-funded between the DOD Breast Cancer Research Program (BCRP) and the NCI Alliance for Clinical Trials in Oncology NCI Community Oncology Research Program (Alliance NCORP). BCRP has invested close to $11M between the two partnering awards on this clinical trial. Women who carry a germline BRCA1 mutation have a high (50%-80%) lifetime risk of developing breast cancer, and the majority of these tumors are aggressive triple-negative breast cancer. The goal of this study is to determine if inhibition of RANK ligand with denosumab is an effective treatment for the primary prevention of breast cancer in women with a germline mutation in the BRCA1 gene, and expands upon the existing Australian BRCA-D denosumab study led by Dr. Geoffrey Lindeman, who is a Co-Investigator on this trial. The BCRP-funded trial will recruit 2,918 subjects from the United States, Australia, Austria, Germany, Israel, Spain, and the United Kingdom. In addition to assessing primary prevention, the study will also assess quality of life, changes in breast density, the impact of denosumab on the tumor phenotype and molecular profile, and whether serum osteoprotegrin levels are associated with breast cancer risk.

Bridging Advanced Developments for Exceptional Rehabilitation Consortium

BADER
The BADER Consortium deliberately made it easy for military and civilian scientists to build meaningful partnerships. The Consortium assembled experienced and early career researchers; added experts in biomechanics, biostatistics, and patient outcomes; and promoted a team research model.

The Bridging Advanced Developments for Exceptional Rehabilitation (BADER) Consortium, led by Dr. Steven Stanhope of the University of Delaware, executed eight research projects and supported the advancement of orthopaedic rehabilitation research capabilities at DOD Military Treatment Facilities (MTFs) and VA sites. The overarching goal of the Consortium was to partner academic institutions with MTFs and VA sites to strengthen and support evidence-based orthopaedic rehabilitation care that results in optimal functional outcomes for Service members with limb loss and limb difference. BADER was a partnership of core civilian trauma centers, four MTFs, and more than 100 affiliates throughout the US, unified to identify and address critical issues challenging the recovery of combat and civilian trauma patients. Over $20M has been invested in the BADER Consortium, which has funded generated 45 published manuscripts and obtained $20.8M in funding for 16 additional projects. In addition, the BADER Consortium partnered on two issues of Military Medicine, the International Journal of AMSUS: “The New Normal of Military Orthopaedic and Rehabilitative Care,” and “Raising the Bar: Extremity Trauma Care.” Both issues focused on partnership and innovation that is taking place in today’s Military Health System and how the military and civilian sectors are flexing to care for Service members with orthopedic combat injuries. Several notable outcomes of the BADER include a university-MTF-industry partnership which developed a real-time biofeedback system that is integrated into clinical care and assists with gait retraining; a university-VA partnership which will extend the findings and apply results of a fall-prevention study to the civilian clinical setting; research efforts initiated on-board aircraft carriers will reach beyond this setting to military land-based clinical rehabilitation sites; and an extensive study of patient self-reported outcomes originally focused on MTFs now includes several community-based civilian rehabilitation facilities.

Concussion Assessment, Research, and Education Consortium

CARE
A joint research effort dedicated to studying the natural history of sport-related concussion in order to better understand the development and trajectory of recovery from concussion.

The National Collegiate Athletic Association (NCAA)–DOD Grand Alliance Concussion Assessment, Research, and Education (CARE) Consortium is a joint research effort dedicated to studying the natural history of sport-related concussion in order to better understand the development and trajectory of recovery from concussion. The CARE Consortium is focused on studying the natural history of concussion through a multi-site, longitudinal investigation of concussive and repetitive head impacts in NCAA student athletes and Service academy cadets, while also testing impact sensor technologies, studying potential biomarkers, and evaluating concussion with advanced neuroimaging. The original project aimed at investigating the acute effects of concussion started in 2014 and enrolled almost 40,000 student athletes and Service academy cadets at 30 performance sites (26 NCAA universities and 4 Service academies). The second project designed to delineate the intermediate effects of concussion started in 2018 and has already enrolled over 13,000 athletes and cadets. Almost $30M from the DOD has been invested in the consortium, which is led by Dr. Tom McAllister at Indiana University, with contributions from co-investigators, Dr. Steve Broglio at the University of Michigan and Dr. Mike McCrea at the Medical College of Wisconsin. Dr. Paul Pasquina at Uniformed Services University joined as a co-investigator for the second project. The data the CARE Consortium has and will continue to collect will allow scientists to develop evidence-based approaches to understanding the risks, management, and possible treatment strategies for concussion. Data from the study are submitted to the Federal Interagency Traumatic Brain Injury Research (FITBIR) informatics system and will be released to the public at project completion. The studies performed by the consortium have been presented in several forums, and data from the CARE Consortium have been included in several publications. Full research articles and more information can be found at http://careconsortium.net/.

The Consortium to Alleviate Post-Traumatic Stress Disorder

CAP
CAP has two main objectives: (1) focusing on the advancement of treatment strategies for PTSD, including interventions for early, chronic, and latent onset cases, and (2) identifying and confirming clinically relevant biomarkers as diagnostic and prognostic indicators of PTSD and co-occurring disorders.

The Consortium to Alleviate Post-Traumatic Stress Disorder (CAP) is a cutting-edge, joint VA and DOD effort to understand and treat PTSD and related conditions in active duty military Service members and Veterans. With a total funding of about $20M, CAP has assembled an unprecedented collaboration of highly qualified researchers and clinicians with expertise in PTSD, neuroscience, genetics, TBI, research in military settings, and comorbid conditions such as depression, sleep disturbances, and substance abuse. CAP is led by Director Dr. Alan Peterson, a retired US Air Force Lieutenant Colonel and clinical psychologist who has personally treated Service members suffering from PTSD symptoms on the battlefields of Iraq. Dr. Peterson is located at the University of Texas Health Science Center San Antonio and the South Texas Veterans Health Care System. The Co-Director of CAP, Dr. Terry Keane of the VA Boston Healthcare System and Boston University, is the Director of the Behavioral Science Division of the National Center for PTSD. The CAP coordinating center is responsible for administration of the consortium, which is distributed among the University of Texas Health Science Center San Antonio, South Texas Veterans Health Care System, VA Boston Healthcare System, Boston University, and Duke University. In addition, CAP has funded core facilities to augment the studies: an Assessment Core, a Biomarkers and Genomics Core, and a Data Management and Biostatistics Core. Numerous VA, academic, and military institutions across the United States participate in CAP. Eleven studies have been approved for implementation by the CAP Government Steering Committee, including two biomarker studies, six randomized clinical trials, and three pilot projects. Five of eleven CAP studies are successfully completed. Over 1,000 Service members and Veterans received gold-standard assessments and high-quality treatments delivered by CAP clinical teams. Additional information can be found at https://patriot.uthscsa.edu/strongstar/.

Detection of Early Lung Cancer Among Military Personnel Consortium

DECAMP
The DECAMP consortium is focused on developing and validating molecular biomarkers that can serve as effective diagnostic and screening tools for lung cancer in high-risk military and Veteran populations.

The Detection of Early Lung Cancer Among Military Personnel (DECAMP) Consortium led by Dr. Avrum Spira of Boston University, was designed to develop and validate biomarkers that could be used to improve the early detection of lung cancer among military personnel, military family members, and Veterans believed to be at high risk. About $13M has been invested in the consortium, which is a multidisciplinary and

translational research program that includes seven VA hospitals, three MTFs, and two academic hospitals as clinical study sites, as well as several molecular biomarker laboratories, along with Biostatics, Bioinformatics, Pathology, and Biorepository Cores. The Biostatistics and Data Management Center handles the clinical trial infrastructure, protocol development, clinical trial data management, quality assurance, regulatory compliance, imaging analysis, and site management. The Lung Cancer Research Program's (LCRP's) direct support of DECAMP ended in March 2019; however, Dr. Spira successfully leveraged the DOD funding he received from the LCRP to receive additional federal and industry support, with significant portions of these new investments being invested in DECAMP infrastructure. DECAMP has two projects ongoing at all sites: one is focused on validating a number of airway and blood-based molecular biomarkers that can distinguish benign vs. malignant lung diseases among smokers with indeterminate pulmonary nodules found on chest-computed tomography scans; the second is focused on developing and testing new noninvasive molecular biomarkers in the airway and blood to identify those smokers at highest risk for developing lung cancer. Samples from the DECAMP patients were used to help validate a commercially available (Affymetrix) bronchial genomic classifier that was developed by the PI and collaborators to facilitate diagnosis of lung cancer in patients with indeterminate lung nodules. Further discovery efforts with the DECAMP patient samples have led to preliminary data on a number of other potential biomarkers and biomarker panels. In addition, the new federal and industry support has allowed one of the projects to be expanded to support the collection of patient tumor samples, increasing the value of the samples and data already collected, and allowing for matching of biomarkers in existing samples to actual cancer tissue. The significant investments from industry and other federal agencies, including independent awards managed by CDMRP, are ensuring the consortium continues on beyond the original LCRP investment. As enrollment wraps up in the coming years, samples will be made available to the research community in the hopes that new biomarkers can be discovered and validated. Continued involvement with the MTFs is being pursued, and an agreement formalizing this relationship is expected in the near future.

The Gulf War Illness Clinical Trials and Interventions Consortium

In FY18, Nova Southeastern University (NSU) was awarded a Clinical Consortium Award totaling about $8M to create a network of institutions and associated infrastructure focused on executing collaborative clinical trials, through Phase II, for the management of GWI. The Gulf War Illness Clinical Trials and Interventions Consortium (GWICTIC) aims to unify the expertise developed through past GWIRP consortium funding based at NSU and Boston University by establishing a platform for implementing clinical trials of interventions specifically targeting neuro-inflammation, previously identified biologic markers of disease activity, and mechanisms of homeostatic reset. The GWICTIC consists of an Operations Center based at NSU with support from four Core facilities: Neuroscience (Boston University); Biomarkers (NSU); Computational Modeling (NSU); and Study Management and Biostatistics (RTI International). The GWICTIC will also unite its GWI expertise and infrastructure with that found within the VA War-Related Illness and Injury Study Centers, a multisite national clinical and research program within the VA healthcare system, providing a link to the VA's recruitment resources and expert clinical investigators. This collaborative team will develop a foundation of scalable infrastructure and management that will facilitate a rapid and effective pathway for moving GWI therapeutic investigations from Phase I to Phase III.

GWICTIC
The GWICTIC aims to unify the expertise developed through past GWIRP consortium funding by establishing a platform for implementing clinical trials.

The Long-Term Impact of Military-Relevant Brain Injury Consortium

The Long-Term Impact of Military-Relevant Brain Injury Consortium (LIMBIC) is a joint DOD and VA effort which builds upon the work of the Chronic Effects of Neurotrauma Consortium (CENC) and is dedicated to establishing a comprehensive research network focused on understanding the chronic sequelae associated with neurotrauma, primarily focused on combat-related and military-relevant mTBI/concussion. This includes establishing the association, causality, diagnostic indicators, and treatment/rehabilitation trajectories of mTBI and potential relationships to neurodegeneration and other comorbidities. The LIMBIC is led by PI Dr. David Cifu at Virginia Commonwealth University. The DOD's contribution to the LIMBIC effort is $25M over a 5-year period of performance, complementing a VA funding investment. The LIMBIC leverages a diverse and comprehensive cadre of research collaborators and sites in 13 major VA TBI-Polytrauma Centers, 11 DOD-Defense and Veterans Brain Injury Center facilities, and 15 academic research centers, along with established links with researchers to provide a pipeline for referral of participants. Six studies were initiated spanning efforts in the areas of epidemiology, genetics and epigenetics, neuroimaging, prognostic modeling, phenotyping, and economics. The centerpiece of the LIMBIC is a large observational cohort study comprehensively examining

LIMBIC
The consortium's efforts will characterize the complexities of chronic mTBI in order to improve prognosis and care of Service members and Veterans.

the long-term consequences of combat-related mTBI in Service members and Veterans from Operation Iraqi Freedom, Operation Enduring Freedom, and Operation New Dawn conflicts. LIMBIC leverages a large, well-characterized, geographically dispersed study cohort, established under the CENC, that can be leveraged in other studies seeking to address mTBI in Service members and Veterans. LIMBIC leverages current and past funding efforts across numerous government agencies to effectively target studies to meet current and evolving research priorities in the field. Additional information can be found at https://www.limbic-cenc.org.

Major Extremity Trauma and Rehabilitation Consortium (Formerly the Major Extremity Trauma Research Consortium)

METRC
The mission of METRC is to produce the evidence needed to establish better treatment guidelines for the optimal care of the Wounded Warrior and ultimately improve the clinical, functional, and quality-of-life outcomes of both Service members and civilians who sustain high-energy trauma to the extremities.

The Major Extremity Trauma Research Consortium (METRC) was established in 2009 with funding from the DOD and the Orthopaedic Extremity Trauma Research Program (at United States Army Institute of Surgical Research). In 2010, the consortium expanded in size and scope through a cooperative agreement with the DOD's Peer Reviewed Orthopaedic Research Program (PRORP), which funded METRC 2. In 2016, METRC 3 was selected for funding via the competitive FY15 PRORP Orthopaedic Care and Rehabilitation Consortium Award PA. With the FY15 award, METRC's historically acute care focus shifted to incorporate rehabilitation Focus Areas, leading to the newly titled Major Extremity Trauma and Rehabilitation Consortium. Through the METRC 2 and METRC 3 awards, the consortium received over $52M in support of 10 clinical studies. In addition, numerous studies associated with METRC or using the METRC Coordinating Center are also being conducted. In 2017, METRC received funding through a FY16 Joint Warfighter Medical Research Program award to support the continuation of two METRC 2 studies and the development and dissemination of Clinical Practice Guidelines and Appropriate Use Criteria in six areas relevant to the treatment of severe extremity trauma. To date, METRC, in collaboration with the American Academy of Orthopaedic Surgeons has published Clinical Practice Guidelines and Appropriate Use Criterias for Management of Acute Compartment Syndrome and Limb Salvage or Early Amputation. A Clinical Practice Guideline for Evaluation of Psychosocial Factors Influencing Recovery from Adult Orthopaedic Trauma was also published.

The METRC Coordinating Center is located at the Johns Hopkins Bloomberg School of Public Health and collaborates with MTFs and civilian trauma centers to conduct multi-center clinical studies relevant to the treatment and outcomes of orthopaedic trauma. More than 70 clinical centers in the US and Canada have enrolled at least one participant in a METRC study.

More information regarding the consortium, METRC studies, and study results can be found at https://metrc.org/.

Military Suicide Research Consortium

MSRC
This USAMRDC funded research aims to enhance the military's ability to quickly identify those at risk for suicide and provide effective evidence-based prevention, treatment, and postvention strategies.

In response to the high rate of suicide among military personnel, the Military Suicide Research Consortium (MSRC) was created in FY10 with DHP funding as a part of an ongoing strategy to synchronize and leverage the DOD and civilian efforts of implementing a multidisciplinary approach to suicide prevention. Drs. Thomas Joiner and Peter Gutierrez from Florida State University and the Rocky Mountain Mental Illness Research, Education and Clinical Center, Denver, Colorado, respectively, co-direct the consortium, which has received approximately $65M in funding. Oversight provided by a Military External Advisory Board ensures relevance and responsiveness to stakeholder needs.

The MSRC has funded 51 studies at numerous military, VA, and civilian sites, of which 18 remain ongoing, and many of these studies have yielded important results. Postdoctoral Pilot Projects and Dissertation Completion Awards have also been funded as part of the MSRC's training program. A Dissemination and Implementation Core was added to the consortium in FY16 to promote the dissemination and implementation of practical, evidence-based strategies resulting from MSRC-funded studies.

The MSRC developed a database to capture Common Data Elements (CDEs) and Common Demographics that are consistent across all projects, which allows for secondary analysis of aggregate data across funded studies. At this time, data from more than 6,500 participants are publicly available to researchers who request access to the data.

For more information about the MSRC and its funded studies, please visit https://msrc.fsu.edu/.

Neurofibromatosis Clinical Trials Consortium

The DOD Neurofibromatosis Research Program (NFRP) established the Neurofibromatosis Clinical Trials Consortium (NFCTC) in 2006 to develop and perform clinical trials for the treatment of neurofibromatosis (NF) complications in children and adults. The NFCTC received additional funding in 2011 and 2016 for a total of approximately $21M in funding. The group of high-profile investigators work collaboratively to develop clinical trials for the treatment of various NF complications, including plexiform neurofibromas, cognitive disorders, low-grade gliomas, vestibular schwannomas, schwannomatosis, tibial pseudarthrosis, and malignant peripheral nerve sheath tumors. The consortium is composed of an Operations Center based at the University of Alabama at Birmingham, 15 clinical sites, and 9 collaborating sites. The Operations Center is responsible for providing administration, data management, and statistical support for the consortium. Each of the clinical and collaborating sites were selected for their expertise in the treatment and management of NF, as well as an established patient population available for clinical trials. Under the direction of Dr. Bruce Korf at the Operations Center, the group has rapidly moved promising therapeutics for NF into clinical trials. Information on the clinical trials and resulting publications can be found at https://www.uab.edu/nfconsortium/ and at https://cdmrp.army.mil/nfrp/consortium/nfrpctc.

NFCTC
To date, the NFCTC has successfully initiated nine clinical trials and supported four additional trials. The NFRP has funded the Clinical Trial Consortium Award in FY06, FY11, and FY16.

Ovarian Cancer Academy

Since FY09, the Ovarian Cancer Academy (OCA) has brought together talented and highly committed Early-Career Investigators (ECIs) with their mentors and Academy Leadership to fulfill the OCRPs vision of a unique, virtual OCA that supports the development of career ovarian cancer researchers who will go on to help treat and cure the disease. In FY19, Dr. Nita Maihle of University of Mississippi Medical Center and Dr. Douglas Levine of New York University Langone Medical Center, were competitively selected to serve as Dean and Assistant Dean for a second term. Additionally, two new FY19 ECI-mentor pairs were welcomed into the OCA bringing the number of currently active OCA ECI awards (FY13-FY19) to 16. To date, $27M has been invested in the Academy. The OCA ECIs have demonstrated remarkable progress, resulting in 627 publications focused on ovarian and other gynecologic cancers. Their growth as independent, committed ovarian cancer researchers is evident in their 163 funded grants, totaling approximately $53M as well as their service on the editorial boards of scientific journals and on panel groups for women's cancer foundations. The annual OCA in-person workshop held at Atlanta in September 2019 included an onsite collaborative meeting with staff at the Centers for Disease Control and Prevention, interaction with survivors, presentations by regional medical entities interested in collaborations with the OCA, as well as a mock study section review of grants. The OCA website http://www.ovariancanceracademy.org/ continues to inform the public about OCA accomplishments and has a private interactive platform which allows the ECIs and OCA leadership to collaborate effectively.

OCA
The OCRP envisions that the synergy produced from sharing information, ideas, and research findings, as well as the substantial research funding provided to the ECIs, will create opportunities to establish them as the next generation of successful and highly respected ovarian cancer researchers.

Ovarian Cancer Consortium

Early ovarian cancer usually has no obvious symptoms, and currently there is no sufficiently accurate screening test for the early detection of ovarian cancer in average-risk women. To address this, the $12M FY10 Ovarian Cancer Consortium Award was executed by a multi-institutional team originally led by Dr. Robert Kurman and finished out by Dr. Tian-Li Wang of Johns Hopkins University, with collaborators at the University of Toronto, Yale, and New York University's Langone Medical Center.

Ovarian Cancer Consortium
Data from this consortium will ultimately help to shape prevention and early detection approaches for ovarian cancer.

The Ovarian Cancer Consortium completed a substantial body of work evaluating the origin of high-grade serous carcinomas (HGSCs) in order to understand the precursor lesion and early changes associated with ovarian cancer. The team demonstrated that serous tubal intraepithelial carcinoma (STIC) is the precursor of HGSCs. They developed and validated an algorithm for the diagnosis of STICs. The team also uncovered that ovarian cancer cells have more commonalities with the cells covering the fimbria of the fallopian tubes, suggesting origin in the fallopian tube, rather than the previously believed ovaries. Uncertainty still exists as to whether the cells that develop into ovarian cancer become malignant in the fallopian tubes or if they circulate to other organs first.

The consortium was highly successful and their results could have major implications for early detection. Publicly available data, shared reagents, the algorithm for STICs diagnosis, and other information are curated in www.ovariancancerprevention.org, the consortium website. The OCRP continues to strive towards the goal of an early detection screening tool for ovarian cancer, and the Ovarian Cancer Omics Consortium Development Award will continue this effort and build upon the knowledge uncovered by the Ovarian Cancer Consortium.

Ovarian Cancer Omics Consortium Development Award

Three OCRP Omics Consortium Development Awards (OMICS-CDA) were made in 2019. Dr. Kunle Odunsi leads the Health Research Inc.'s "DOD and SPORE Ovarian Cancer Omics Consortium," Dr. Rudolf Kaaks leads the Deutsches Krebsforschungszentrum's effort titled "PREDICT: Prospective Early Detection Consortium for Ovarian Cancer," and Dr. Douglas Levine of the New York University School of Medicine rounds out this esteemed collective of ovarian cancer researchers as the PI of the "DOD Omics Consortium to Study the Origins of Ovarian Cancer." This award supports multi-institutional research efforts specifically focus on the compilation of large datasets to study the origin of ovarian cancer disease, with an emphasis on the early detection and screening of ovarian cancer. The OMICS-CDA mechanism is the first stage of a two-stage approach; it enables the consortia to lay the groundwork and develop proof-of-concept for the second stage or the Omics Consortium Award, a separate future funding opportunity which will support the execution of the subsequent larger research project.

OMICS-CDA
This consortium development award was awarded to three teams. It lays the groundwork for the future Omics Consortium Award. The effort focuses on the compilation of datasets to study the origin of ovarian cancer.

In addition to dedicated ovarian cancer researchers, each consortia team includes an Early-Career Investigator, an ovarian cancer patient/survivor and an epidemiologist, all of whom are integrally involved throughout the planning and implementation of the research project. Given the high degree of expertise and well roundedness of the consortia teams, as well as the breadth of these distinct approaches, there is much confidence that they will succeed in this Consortium Development stage, meet the requirements of applying to the upcoming Omics Consortium Award, and understand the origin(s) of ovarian cancer and improve screening and early detection.

Ovarian Cancer Outcomes Consortia

The two FY15 Outcomes Consortium Award teams led by Dr. Malcom Pike of Memorial Sloan Kettering Cancer Center and Dr. Michael Birrer, while he was at the University of Alabama, are focused on identifying and understanding predictors of disease outcome in ovarian cancer patients and moving toward tailored therapies that maximize patient survival and quality of life. Close to $9M has been invested in the teams, and both groups are midway through their award span and processing significant amounts of data while working closely with their team's integrated consumer advocates as well as with the DOD Gynecologic Oncology Center of Excellence to maintain focus on meaningful outcomes for ovarian cancer patients and survivors.

Ovarian Cancer Outcomes Consortia
Two teams were funded to identify predictors of long-term survival to enable tailored therapies that maximize patient survival and quality of life.

The Multidisciplinary Ovarian Cancer Outcomes Group is studying the role of the immune response; genetics, especially those related to DNA repair; and epidemiological and lifestyle factors that contribute to long-term survival in women diagnosed with advanced-stage ovarian cancer. New data from this team indicates that anti-inflammation-related exposures (pre-diagnosis) are associated with improved survival. As these exposures, such as menopausal hormone therapy, are modifiable, it offers hope for increased survival. They also recently published on ovarian cancer survivors' views of factors that influenced their long-term survival, which include lifestyle modification, motivation and persistence, strong life purpose, and strong support systems.

The Ovarian Cancer Consortium for the Genomic, Epigenetic, and Quality of Life Characteristics of Long-Term Survival, is focused on finding predictive biomarkers that will help in the design of individualized care for patients with ovarian cancer who were diagnosed with early-stage disease. Using data from a longitudinal analysis of quality of life their initial analysis indicates long-term survivors were significantly younger at diagnosis, had lower-grade disease, and had significantly higher/better social well-being, with fewer ovarian cancer-specific concerns compared to short- and intermediate-term survivors.

Pain Management Collaboratory

Started in FY17, the Pain Management Collaboratory (PMC) is an interagency partnership between the NIH, the DOD, and the VA that supports research addressing the needs of the Service member and Veteran communities living with and managing pain. This $81M 6-year collaborative multi-institutional research initiative focuses on the development, implementation, and testing of cost-effective, large-scale, pragmatic clinical trials of non-pharmacological approaches to pain management. The PMC includes 11 individual clinical trials and a coordinating center, which supports the projects by providing best practices, tools, data, and other resources.

PMC
Additional information regarding the PMC can be found at https://painmanagementcollaboratory.org/

The four CDMRP-managed projects, funded by the DOD, will provide important information about the feasibility, acceptability, safety, and effectiveness of non-pharmacological approaches in treating pain. Types of approaches being studied include Mindfulness (study led by Dr. Diana Burgess at the Minneapolis VA Health Care System), Psychologically-Informed Physical Therapy (study led by Dr. Shawn Farrokhi at the Naval Medical Center, San Diego), Behavioral Health Consultants (study led by Dr. Donald McGeary at the University of Texas Health Science Center at San Antonio), and Percutaneous Peripheral Nerve Stimulation (study led by Dr. Brian Ilfield at the University of California, San Diego). In March 2020, all projects received satisfactory evaluation of the initial 2-year pilot study and planning phase and were approved to move forward with implementation of the large-scale demonstration projects. Enrollment of study participants in sponsored pragmatic clinical trials is anticipated to begin during the 2020 calendar year.

Pharmacotherapies for Alcohol and Substance Abuse Consortium

In 2015, the Alcohol and Substance Abuse Disorders Research Program established the Pharmacotherapies for Alcohol and Substance Abuse (PASA) Consortium. The Consortium is led by Dr. Tracy Nolen from RTI International, in collaboration with Baylor College of Medicine. Almost $28M has been invested in the PASA Consortium, which has three aims in developing pharmacotherapies for Alcohol and Substance Use Disorders (ASUDs), particularly in the context of the reciprocal relationship between ASUDs versus stress and anxiety, as manifested in PTSD/TBI: (1) discover novel medications and combination medications for ASUDs and PTSD/TBI; (2) develop these medications through a rational proof-of-concept pipeline model; and (3) conduct Phase II preliminary efficacy trials of potential medication combinations in optimal target populations and explore functional genetic polymorphisms for matching patients to these medications. There are six active studies (two pre-clinical, two clinical trials at VA Medical Centers, and two planning grants) and one active Investigational New Drug (IND). PASA-funded studies have examined the pharmacotherapeutics for ASUD with comorbid PTSD/TBI. The compounds that have shown potential and are of interest to Pharma are those that align with the mechanisms of action of Kappa Opioid antagonists and GABA-B agonists. Two compounds have been transitioned to Pharma for further development, CERC 501 owned by Jansen and ASP8062 owned by Astellas. The ASADRP did not receive a congressional appropriation in FY20. The PASA award's current period of performance ends on September 14, 2023. A statement of work and budget are in place to fund the remaining sub-awards and manage the PASA consortium through completion.

PASA
Additional information regarding the PASA Consortium can be found at https://pasa.rti.org/.

Prostate Cancer Biorepository Network

The Prostate Cancer Biorepository Network (PCBN) is a bioresource that provides prostate cancer tissue and other patient samples to prostate cancer investigators worldwide. Established in 2010, it currently includes the combined resources of the five Prostate Cancer Research Program (PCRP)-funded sites – Johns Hopkins University, New York University, the University of Washington, the Institute of Cancer Research in London, and Washington University in St. Louis – which strive to provide high-quality, well-annotated specimens obtained in a systematic, reproducible fashion using optimized and standardized protocols.

PCBN
The PCBN has established itself as the largest, most comprehensive prostate cancer biorepository in the world.

Each site specializes in different types of patient samples and provides complementary resources including: metastatic tissue (rapid autopsy and lymph node); biospecimens with long-term follow-up for biochemical recurrence, metastasis and death, active surveillance, hormone, and neoadjuvant therapy; tissues from African American men; and patient-derived xenograft models.

Since its inception, the PCBN has distributed more than 5,800 patient samples to prostate cancer investigators. Studies utilizing PCBN samples have led to 80 manuscripts published in peer reviewed journals, and have helped to clinically validate at least 26 prostate cancer biomarkers, including the AR-V7 marker. The PCBN's efforts have also extended beyond sample acquisition and distribution through the pursuit of biospecimen science, which addresses important questions related to biospecimen quality and stability, establishing PCBN as a leader in the biobanking field (for additional information, see http://prostatebiorepository.org/).

Prostate Cancer Clinical Trials Consortium

PCCTC
The PCCTC has established itself as the nation's premier prostate cancer clinical trials group and remains poised to make a significant impact on patients' lives by keeping the drug pipeline primed with promising novel agents.

The Prostate Cancer Clinical Trials Consortium (PCCTC) was originally established in 2005 through the collective efforts of the PCRP and the Prostate Cancer Foundation. In 2014, the PCCTC became a limited liability company (Prostate Cancer Clinical Trials Consortium, LLC) and today boasts 10 PCRP-funded clinical research sites and over 50 participating affiliate sites. In total, over $72M has been invested in the consortium. The goal was to combine the work of leading investigators with the unique institutional resources of outstanding clinical research sites across the US to bring to market high-impact, novel therapeutic interventions that would ultimately and significantly decrease the impact of prostate cancer. The PCCTC's efforts have helped bring numerous potential new therapeutics into Phase III clinical trials, with three agents having now received approval by the FDA: abiraterone acetate, enzalutamide, and apalutamide.

The consortium's successful acceleration and streamlining of the clinical trial process has enabled the PCCTC to approve 248 clinical trials for activation, 172 of which have been completed (closed to accrual), and enroll more than 7,800 patients to these trials; 10% representing patients from disproportionately affected populations. The consortium is also at the forefront of the precision medicine arena, incorporating liquid biopsies to identify distinct prostate cancer subtypes to inform treatment decisions, and has provided recommendations for considering the use of germline genetic testing in therapeutic or clinical trial purposes. Through the collaborative nature and intellectual synergy of its leadership, the PCCTC remains poised to make a significant impact on patients' lives by keeping the pipeline primed with the most promising novel agents and validated biomarkers (for additional information, see http://pcctc.org/).

Surgical Timing and Rehabilitation Consortium

STaR
This effort focuses on optimizing both surgical care and rehabilitation for military and civilian patients with MLKIs.

The Surgical Timing and Rehabilitation (STaR) Consortium, led by Dr. James Irrgang of the University of Pittsburgh, is a multi-site clinical effort that will provide scientific evidence to optimize both surgical care and rehabilitation for military and civilian patients with multiple ligament knee injuries (MLKIs). MLKIs represent a spectrum of injury that can create multiple serious complications during treatment. Approximately $4.5M has been invested in the consortium, which is comprised of two separate clinical trials that will determine the most optimal times for surgery and post-operative rehabilitation to increase the rate of return for individuals with MLKIs to their preinjury physical function and level of activity. The first aim is to determine the combined effects of early versus delayed timing of surgery and rehabilitation on the time it takes an individual to return to their pre-injury status and activity. The second aim is to investigate the effects of early versus delayed rehabilitation. This second aim will include participants with MLKIs, for which the timing of surgery cannot be randomized for any number of reasons. In order to provide the support structure and scientific evidence needed to address the scientific question, the University of Pittsburgh has brought together a robust governance structure and highly accomplished research study team. Research participants will be recruited at a total of 25 clinical sites comprised of 3 US MTFs, 19 US civilian sites, and 3 Canadian sites. PRORP funded the consortium, which was submitted in response to the FY16 PRORP Integrated Clinical Trial Award mechanism. Study enrollment began in 2018. As of April 2020, 109 patients have been enrolled and randomized into STaR trials.

Team Approach to the Prevention and Treatment of Post-Traumatic Epilepsy

The goal of the Team Approach to the Prevention and Treatment of Post-Traumatic Epilepsy (TAPTE) is to establish a multi-center, multi-investigator research team focused on post-traumatic epilepsy (PTE). Under the leadership of Laura Lubbers from Citizens United for Research in Epilepsy (CURE) and funds of $10M, TAPTE will identify new biomarkers that may be the foundation of new clinical trial endpoints for interventions in PTE. Based on previous successes within the epilepsy community, the CURE will use their scientific model to rapidly advance the most promising research in PTE within the research consortium. TAPTE has built a "critical mass" of investigators with similar research interests and diverse backgrounds to address and execute PTE research. The investigative team will work closely with CURE, NIH, CDMRP, and USAMRDC, who proactively monitor research progress and advise the consortium on which directions to take to ensure ultimate success. Research was recently initiated, and the lead investigators continue to build their research partnerships.

TAPTE
TAPTE's goal is to establish a multi-center, multi-investigator research team focused on PTE that will rapidly translate patient-relevant findings at the molecular, cellular, and systems level into novel therapies.

Traumatic Brain Injury Endpoints Development Initiative

The TBI Endpoints Development (TED) Initiative established a collaborative, multi-disciplinary research team to advance clinically validated endpoints that can support regulatory approvals for trials involving the diagnosis and treatment of mild to moderate TBI, a complex and heterogeneous disease. These endpoints include clinical outcome assessments, blood-based biomarkers, and neuroimaging biomarkers. Currently there are limited devices with FDA-cleared uses in TBI-specific diagnostics. There are also no FDA-approved drugs for TBI. Over $17M was invested in the TED team, which is led by PI Dr. Geoff Manley at the University of California, San Francisco. The TED team leverages existing research infrastructure, clinical networks, and government partnerships such as the Transforming Research and Clinical Knowledge in TBI, the Concussion Research Consortium, and CENC. Stage I of the TED award focused on establishing a TED database integrating clinical outcomes, imaging, and biomarker data from ongoing and legacy TBI studies across civilian, military, and sports cohorts. Stage II activities are focused on advancing regulatory readiness of candidate clinical outcome assessments and biomarker efforts from Stage I. The TED initiative has been recognized by the FDA through letters of support and recognition. A software plug-in, the OsiriX CDE Software Module, developed under the TED initiative was qualified by the FDA's Medical Device Development Tools program as a biomarker test for TBI and is the first qualified TBI tool under this program. This tool will enable researchers to improve TBI-related clinical trial design by refining eligibility criteria. The long-term goal of the TED initiative is to be able to empower TBI researchers and clinicians with tools that can maximize patient outcomes based on disease trajectory. More information about the TED initiative can be found at https://tbiendpoints.ucsf.edu/.

TED
This initiative leverages collaborations among 23 academic institutions, as well as a number of government, private, and philanthropic organizations along with data from a number of other current and past funding efforts spanning several government agencies.

Participation in other Federal and Non-Federal Organization Efforts

Partnering with multiple federal and non-federal committees to compare research portfolios, identify gaps in research funding, and improve existing research efforts is a major effort of CDMRP. We invite members of other federal and non-federal agencies to participate in the peer and programmatic review processes as well as to serve on review boards to monitor and oversee the progress of awards, which ensures no research effort is duplicated and provides an opportunity to encourage complementary investment strategies. Examples of interagency collaborations include, but are not limited to, the following:

Participation in Other Federal and Non-Federal Organization Efforts
These interagency collaborations strive toward synergy with other agencies and diversification of funded research portfolios, underscoring the importance of research coordination efforts.

Advisory Committee on Breast Cancer in Young Women

A Centers for Disease Control and Prevention-led committee focused on evidence-based activities designed to prevent breast cancer, particularly among those at heightened risk, as well as to promote the early detection of breast cancer and support of young women who develop the disease.

Amputee Coalition
An organization which seeks to reach out and empower people affected by limb loss to achieve their full potential through education, support, and advocacy, and to promote limb loss prevention. The Amputee Coalition strives to raise awareness about and increase practices to prevent limb loss, ensure that no amputee feels alone through pre- and post-amputation and recovery, and help amputees and their families live life to the fullest after amputation.

Citizens United for Research in Epilepsy
As the leading nongovernmental agency, CURE is fully committed to funding research and other initiatives that will lead the way to cures for epilepsy. CURE's mission is to find a cure for epilepsy by promoting and funding patient-focused research.

The Interdepartmental Health Equity Collaborative
The mission of the Interdepartmental Health Equity Collaborative is to end health disparities by building capacity for equitable policies and programs, cultivating strategy partnerships, and sharing relevant models for action.

Federal Interagency for Research and Development of Blood Products and Related Technologies for Trauma Care and Emergency Preparedness
The Interagency Strategic Plan for R&D of Blood Products and Related Technologies for Trauma Care and Emergency Preparedness is an effort among the DOD and the HHS (specifically NIH/National Heart, Lung, and Blood Institute, Assistant Secretary of Preparedness and Response/Biomedical Advanced Research and Development Authority, and the FDA Office of Counterterrorism and Emerging Threats), in collaboration and coordination with other key US Government stakeholders. The strategic plan aims to improve patient outcomes following combat trauma or mass casualty events and to foster the restoration of health through leveraging of capabilities across agencies and enhanced research targeted toward filling critical gaps in the delivery of blood products, blood-related resources, and technologies.

FITBIR Policy Group
A group composed of stakeholders from the NIH Center for Information Technology, National Institute of Neurological Disorders and Stroke, VA, and USAMRDC that develop and implement policies for the management and execution of the FITBIR informatics system.

FITBIR Working Group
An NIH-sponsored group whose mission is to enhance communication, coordination, and collaboration in the field of TBI across agencies.

Foundation Allied Support Group
A group of national ovarian cancer advocacy organizations that work together to promote collaboration and cooperation among the advocacy groups.

Interagency Autism Coordinating Committee
A federal advisory committee that coordinates efforts within the HHS related to ASD. The Interagency Autism Coordinating Committee helps to ensure that a wide range of ideas and perspectives are represented and discussed in a public forum through the inclusion of both federal and public members.

Interagency Urology Coordinating Committee
A federal advisory committee, facilitated by HHS's National Institute of Diabetes and Digestive and Kidney Disorders, that coordinates the research activities of all national research institutes related to urologic diseases to ensure their adequacy and technical soundness and to provide the exchange of information necessary to maintain adequate coordination.

International Cancer Research Partners
A group of 28 funding partners representing 136 organizations working together to enhance the impact of research to benefit all individuals affected by cancer through global collaboration and strategic coordination. https://www.icrpartnership.org/

International League Against Epilepsy Task Force
The overall goal of this new group will be to examine this topic and recommend how the International League Against Epilepsy can help move forward with a global or international perspective. In the course of this term we expect this Task Force to identify clear goals and the steps that the League can take to realize those goals. The Task Force is composed of national and international experts from both government and academia.

Muscular Dystrophy Coordinating Committee

An NIH-established committee to foster collaboration among federal health programs and activities relevant to the various forms of muscular dystrophy.

National Alzheimer's Project Act

A group that combines federal efforts to coordinate AD and related dementia (ADRD) research. The National Plan for AD/ADRD is updated annually from this interagency collaboration in conjunction with the public-private Advisory Council on Alzheimer's Research, Care, and Services.

Trans-NIH Neurofibromatosis Working Group

An NIH-sponsored group that meets to enhance communication and collaboration about the state of the NF science and progress on funded awards.

Trans-NIH Tuberous Sclerosis Complex Committee

An NIH-sponsored committee that consists of representatives of NIH Institutes that fund tuberous sclerosis complex-related research, the Tuberous Sclerosis Alliance and TSCRP that meets to enhance communication and collaboration between the funding agencies about the state of the science and progress on funded research.

OUR PROGRAMS

The 37 research programs highlighted in this section share many common features, yet each program is unique and emphasizes the specific needs of the research and advocacy communities. These programs are detailed on the following pages.

ALCOHOL AND SUBSTANCE ABUSE DISORDERS RESEARCH PROGRAM

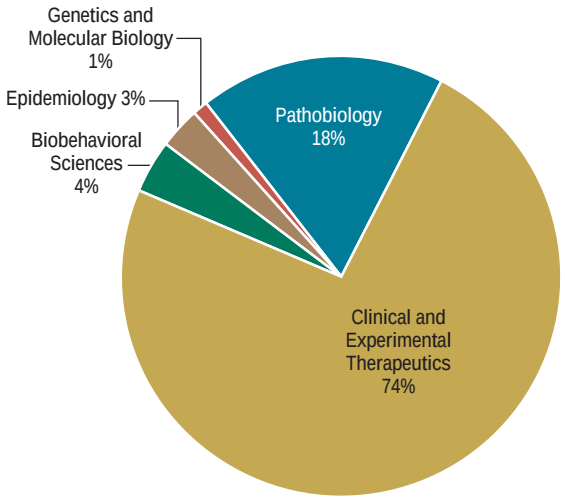
Vision: Decrease the clinical impact of alcohol and substance abuse

Mission: To explore integrated approaches to address alcohol and substance use disorders, especially related to TBI and PTSD, through multidisciplinary, team-based research efforts that translate basic knowledge into enhanced clinical pharmacological treatment protocols for Service members, Veterans and the American public

The program's approach is to organize multidisciplinary, team-based translational research efforts to identify promising compounds, conduct proof-of-principle basic research to determine which compounds are most appropriate for human research trials, and conduct human proof-of-principle trials with promising compounds. If successful, this approach could result in translation of contemporary basic science knowledge into enhanced clinical pharmacological treatment protocols for ASUDs.

Program History

The problem of alcohol and substance abuse is a growing concern among the general public, as well as military personnel and Veterans alike. In 2013 the IOM report,[1] Substance Use Disorders in the US Armed Forces, characterized the overall prevalence of heavy drinking at 20% and the overall prevalence of illicit drug use at 12%. Rates of acute and chronic incident alcohol diagnoses increased from 2001 through 2010, especially for the active duty component. The results indicate the increasing medical burden imposed on the Military Health System by excessive alcohol use. Substance abuse was involved in 30% of the Army's suicide deaths since 2003.[2] Furthermore, ASUDs significantly worsen the hyper-arousal effects of PTSD, a disorder that affects 14% of all previously deployed US military personnel.[3] ASUD may worsen the effects of PTSD in Veterans with chronic TBI. Compared to individuals with PTSD or ASUD alone, those with PTSD and co-existing ASUD exhibit greater severity of PTSD and ASUD symptoms.[4,5] Veterans with both PTSD and ASUD exhibit more persistent, severe, and treatment-resistant symptoms, and are at much higher risk for suicide, than Veterans who have either disorder alone.[6] The 2013 IOM report recommended that the DOD assume leadership to ensure the consistency and quality of treatment services available to those with ASUDs, given the burden of ASUD in the military. The Peer Reviewed Alcohol and Substance Abuse Disorders Research Program (ASADRP) was established in FY10 with a congressional appropriation of $6.375M. Since then, the program has established a network of multidisciplinary, translational research teams with the explicit goal of accelerating the delivery of new or improved treatments for ASUDs; as a result, the ASADRP has distributed a total of $36.075M to relevant research. ASADRP did not receive an appropriation in FY20, but continues to manage currently open awards and remains focused on advancing program goals. The goal of the program is to identify and develop new medications to improve treatment outcomes for ASUDs, especially related to TBI and PTSD.



FY10-FY19 ASADRP Portfolio Investment by Scientific Classification System (SCS) Code (% of total investment)

[1] Institute of Medicine. 2013. Substance Use Disorders in the US Armed Forces. Washington, DC: The National Academies Press. (https://www.ncbi.nlm.nih.gov/books/NBK207280/)
[2] NIDA. 2020. Substance Use and Military Life DrugFacts. *National Institute on Drug Abuse*. 15 Jul. 2020. (https://www.drugabuse.gov/publications/drugfacts/substance-use-military-life)
[3] Acosta JD, Martin LT, Fisher MP, et al. 2012. Assessment of the Content, Design, and Dissemination of the Real Warriors Campaign. Santa Monica, CA: RAND Corporation. (https://www.rand.org/content/dam/rand/pubs/technical_reports/2012/RAND_TR1176.pdf)
[4] Jacobsen LK, Southwick SM, and Kosten TR. 2001. Substance use disorders in patients with posttraumatic stress disorder: A review of the literature. *Am J Psychiatry* 158(8):1184-1190.
[5] Norman SB, Myers US, Wilkins KC, et al. 2012. Review of biological mechanisms and pharmacological treatments of comorbid PTSD and substance use disorder. *Neuropharmacology* 62(2):542–551.
[6] McCarthy E and Petrakis I. 2010. Epidemiology and management of alcohol dependence in individuals with post-traumatic stress disorder. *CNS Drugs* 24(12):997-1007.

The Pharmacotherapies for Alcohol and Substance Abuse Consortium

Abstract Submissions to Military Health System Research Symposium 2020

Effects of A Novel Anti-Fentanyl Vaccine and Buprenorphine in Rats
Colin N. Haile, M.D., Ph.D., University of Houston

Overdose deaths due to opioid use disorder (OUD) or accidental opioid exposure adversely affect Veterans. Fentanyl is a potent drug used clinically to treat pain. Illegal fentanyl use has proven lethal accounting for thousands of overdose deaths. Fentanyl is lethal primarily because it rapidly penetrates the brain. High doses of naloxone are typically used to reverse fentanyl overdose but is often unsuccessful. Development of an anti-fentanyl vaccine could potentially treat OUD and avoid overdose by preventing fentanyl from getting into the brain.

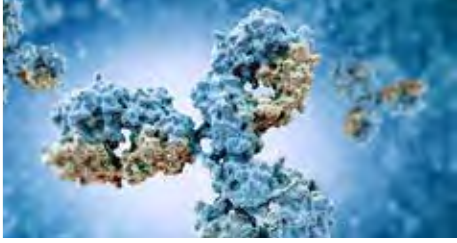
We generated an anti-fentanyl conjugate vaccine that was administered with the adjuvant dmLT to enhance production of anti-fentanyl antibodies. Male and female rats received vehicle or the vaccine followed by boosts at 3 and 6 weeks alone or in combination with buprenorphine that is used to treat OUD in humans. Blood samples were taken and anti-fentanyl antibody levels determined. The analgesic effects of fentanyl were also assessed. Brain levels of fentanyl were quantified at the end of the experiment following administration of a high dose of fentanyl.

Vaccination with the anti-fentanyl vaccine generated significant levels of anti-fentanyl antibodies in both male and female rats. The analgesic effects of fentanyl were completely blocked in vaccinated rats with or without buprenorphine. Buprenorphine administered alone without vaccination also blocked fentanyl's analgesic effects in female, but not completely in male rats. The vaccine protected rats from the lethal effects of a high dose of fentanyl. Compared to controls, greater than 90% of fentanyl was prevented from penetrating the brain in vaccinated rats following fentanyl administration. Data support further development of our anti-fentanyl vaccine for the treatment of OUD and to prevent overdose deaths due to fentanyl.

Pharmacodynamic Interaction Between the Glucocorticoid Receptor Antagonist, PT150, and Ethanol in Healthy Veterans and Civilians
Christopher D. Verrico, Ph.D., Baylor College of Medicine
Dewleen G. Baker, M.D., University of California San Diego

Combat exposure confers risk for new-onset hazardous drinking and a higher likelihood of relapse, as well as for PTSD. Individuals with PTSD fail to contain stress response and reinstate homeostasis, potentially reflecting hypersensitivity of the glucocorticoid receptor (GR). Hypersensitivity of the GR is associated with alcohol use disorder and drinking relapse. Traumatic events and alcohol activate stress pathways, thus targeting steroid hormones or antagonizing receptors that mediate responses is a potential treatment. PT150 (previously ORG 34517) is a highly selective partial-GR competitive antagonist. In a preclinical model, PT150 reduced the severity of alcohol withdrawal and related hypothalamic–pituitary–adrenal (HPA) axis activation without altering blood alcohol levels (BAL).

Dr. Verrico recently completed a Phase I single-site, within-subject, Randomized Controlled Trial (RCT) among 10 adults titled 'PT150 (Formerly ORG34517) as a Potential Treatment for Alcohol Use Disorder – Alcohol Interaction Study.' Before a Phase II outpatient RCT could be planned, the FDA requested this study be conducted to ensure there were no increased safety risks due to PT150 and ethanol interaction. Overall, there were no clinically significant drug-drug interactions on blood pressure, heart rate, adverse events, electrocardiograms, or alcohol-related questionnaires. Additionally, BAL summary measures, including concentration maximum, time to maximum, and area under the curve were similar before and after PT150 exposure. Results indicate that alcohol can be safely consumed in the presence of PT150, suggesting no significant pharmacodynamic interactions, and support future study of PT150.

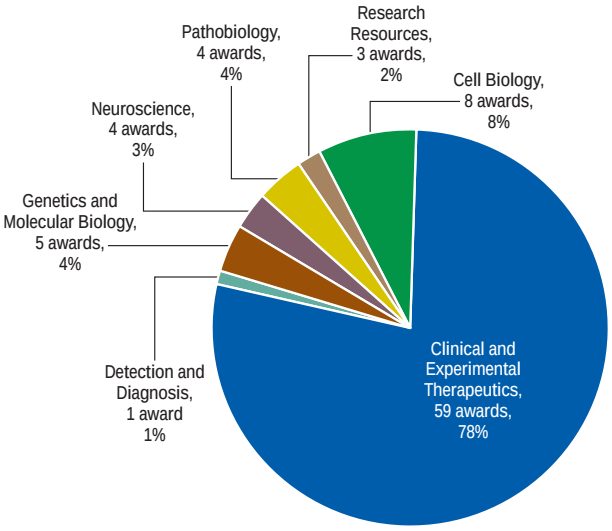


AMYOTROPHIC LATERAL SCLEROSIS RESEARCH PROGRAM

Program History

The Peer Reviewed Amyotrophic Lateral Sclerosis Research Program (ALSRP) was created in 2007 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. Although the ALSRP was not funded in FY08, Congress appropriated funding in FY09 and has continuously provided funding since, with a total appropriation of more than $80M. The overall goal of the program has been to expedite the pathway from bench science to clinical trials for new therapeutic approaches in amyotrophic lateral sclerosis (ALS). Over 80 projects have been funded through FY19, many of which are still in progress. From these funded efforts, four promising new ALS drug candidates have moved into advanced drug development and three have advanced to early-phase clinical trials.

From the inception of the program through FY19, the portfolio has been narrowly focused on therapeutic discovery and preclinical validation research projects, with the intent to identify new ALS drug candidates and move them into advanced drug development. Recent increases in the ALSRP congressional appropriation, from $10M in FY19 to $20M in FY20, have enabled the program to increase investments in innovative and unconventional preclinical therapeutic approaches. In FY20, the ALSRP expanded its mission by offering a mechanism in a more clinical space, the Clinical Development Award, with the intention of leveraging patient-based resources to foster biomarker development, optimizing aspects of current ALS care, and further enriching therapeutic development.



FY07-FY19 ALSRP Portfolio Investment by SCS Code

ALS Impacts US Service Members and Veterans

Research supports the conclusion that people who have served in the military are at a greater risk of developing ALS than those with no history of military Service. Deployment contributing to a risk for ALS was reviewed by the National Academy of Medicine (formally the Institute of Medicine), which concluded in 2006 that an association does exist. Subsequently, the VA implemented regulations to establish a presumption of a Service connection to ALS. The benefits of the treatment-focused research conducted for the ALSRP extend to military Service members, Veterans, military beneficiaries, and the general public.

Vision: **Improve treatment and find a cure for ALS**

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

"In FY20 we distributed a *Mechanisms & Priorities Survey* to crowd-source the collective wisdom of the entire ALS community. Based on the responses, we have prioritized funding of novel innovative ideas through the Therapeutic Idea Award mechanism, provided greater emphasis on biomarker development to improve and de-risk eventual clinical trials, added the new Clinical Development Award mechanism, and emphasized open data and resource sharing, so advances can be rapidly leveraged by the ALS research community."
Lyle Ostrow, M.D., Ph.D., ALSRP Programmatic Panel Chair

Research Highlight

Novel ALS Therapeutic Intervention Shows Promise in Preclinical Trials

Mart Saarma, Ph.D., University of Helsinki
Merja Voutilainen, Ph.D., University of Helsinki

ALS is a devastating neurodegenerative disease characterized by the degeneration of the motor neurons and subsequent rapid deterioration of motor function, muscle atrophy, and eventual paralysis. There is no cure for ALS and currently, therapeutic options are limited. Innovations in treatment are critical to improving the quality of life for ALS patients and their families.

In work funded by a FY17 ALSRP Therapeutic Idea Award, researchers at the University of Helsinki, Finland, led by Dr. Mart Saarma, are working to repurpose a potential Parkinson's disease (PD) treatment for use in ALS patients since the diseases share common pathogenic mechanisms. Cerebral dopamine neurotrophic factor (CDNF) is a novel endoplasmic reticulum (ER) stress regulating protein with neurotrophic activity and a mechanism of action different from conventional neurotrophic factors. CDNF treatment has been shown to protect and restore damaged neurons in rodent models of PD more effectively than any other protein previously tested, and it has shown promising topline results in the ongoing Phase 1-2 clinical trials in patients with PD. In order to investigate and enhance the therapeutic potential of CDNF in ALS, Drs. Saarma, Voutilainen, Sendtner, and Harvey have optimized the dose and delivery system of the protein in ALS animal models. They have now been able to show that a single dose of a novel CDNF variant can increase survival and improve motor coordination in multiple ALS murine models. These treatments, or chronic infusion of this protein over time, also delayed symptom onset and protected motor neurons in the spinal cord. Importantly, these findings were observed even in the most severe animal model tested.

This work was recently published in bioRxivs[1] and is currently under review for peer-reviewed publication. CDNF has been granted an orphan drug status, clearing the pathway for its development into a therapeutic agent for ALS. The research team is hopeful that CDNF holds great promise as a future therapeutic for ALS.

Program Priorities

Preclinical Treatment Discovery
- Animal and cell models
- High-throughput screens
- Identify candidate drug leads
- Measure drug-target engagement

Preclinical Treatment Validation
- Secondary validation and drug delivery
- Optimization of drug properties
- Collect data for FDA submission
- Develop Good Manufacturing Practices methods

Clinical Research New for FY20!
- Encourage use of established ALS patient repositories
- Promote correlation of patient samples with clinical outcomes
- Optimize current ALS clinical care strategies

Research Mechanisms

Therapeutic Idea Award
- FY10–present
- Identify candidate drugs in high-throughput screens
- Validate resulting drug candidates, assess pharmacological properties, and demonstrate effect on intended molecular targets

Therapeutic Development Award
- FY07–present
- Ready candidate drugs for clinical trials by secondary validation, optimization of pharmacological properties, development of manufacturing processes, and compilation of data for FDA submissions
- Develop markers to demonstrate drug actions on intended molecular targets

Clinical Development Award
- New for FY20!
- Leverage human subject-based resources through correlative clinical research to better define subtypes, predict therapeutic response, assess prognosis, and optimize components of current ALS clinical care
- Correlate clinical trial-related biosamples, imaging, or epidemiological data with clinical outcomes

[1] De Lorenzo F, Lüningschrör P, Nam J, et al. (Preprint) 2020. CDNF rescues motor neurons in three animal models of ALS by targeting ER stress. *bioRxiv.* doi: 10.1101/2020.05.05.078618

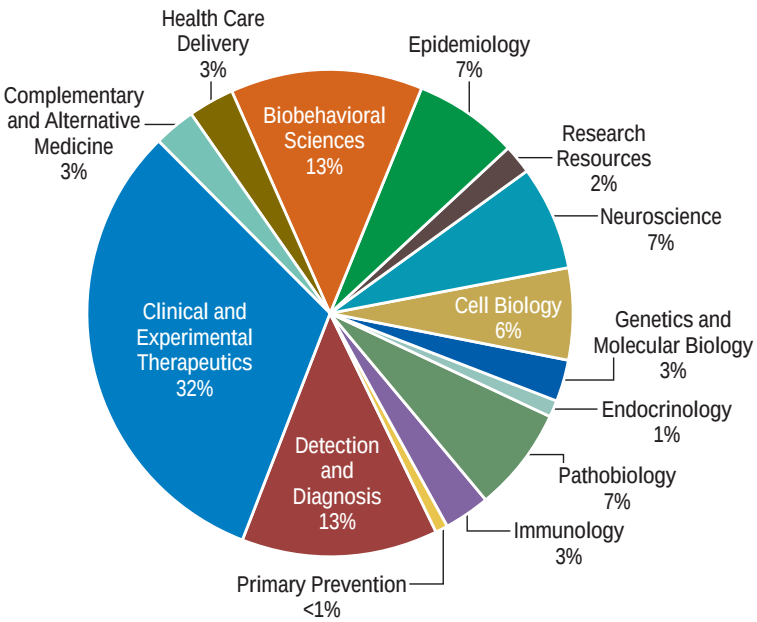
AUTISM RESEARCH PROGRAM

Program History

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

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

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



FY07-FY19 ARP Portfolio Investment by SCS Code

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

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

"It was a real honor to be part of the Autism Research Program Peer Review Panel; I will always be grateful for the Organization for Autism Research for nominating me. Representing the ASD community from both an individual and family perspective (I have two brothers on the spectrum) is important when thinking about funding research with the most impact. The scientific research reviewers are brilliant, and the research that was reviewed was fascinating and powerful."

Cathy Schwallie Farmer, ARP Consumer Reviewer

Funding Research that Targets the Core Symptoms of ASD

Currently, there is no approved pharmacotherapy for the core debilitating symptoms of ASD, which are impaired social communication and repetitive behaviors. The ARP recognizes that the option of pharmacologic interventions could be monumental for many individuals with ASD, allowing them to function better and improve their quality of life. For that reason, pharmacological treatments are an Area of Interest for the ARP. Recently funded projects in this area are highlighted below.

The Development of Novel Drugs to Treat the Core Symptoms of ASD

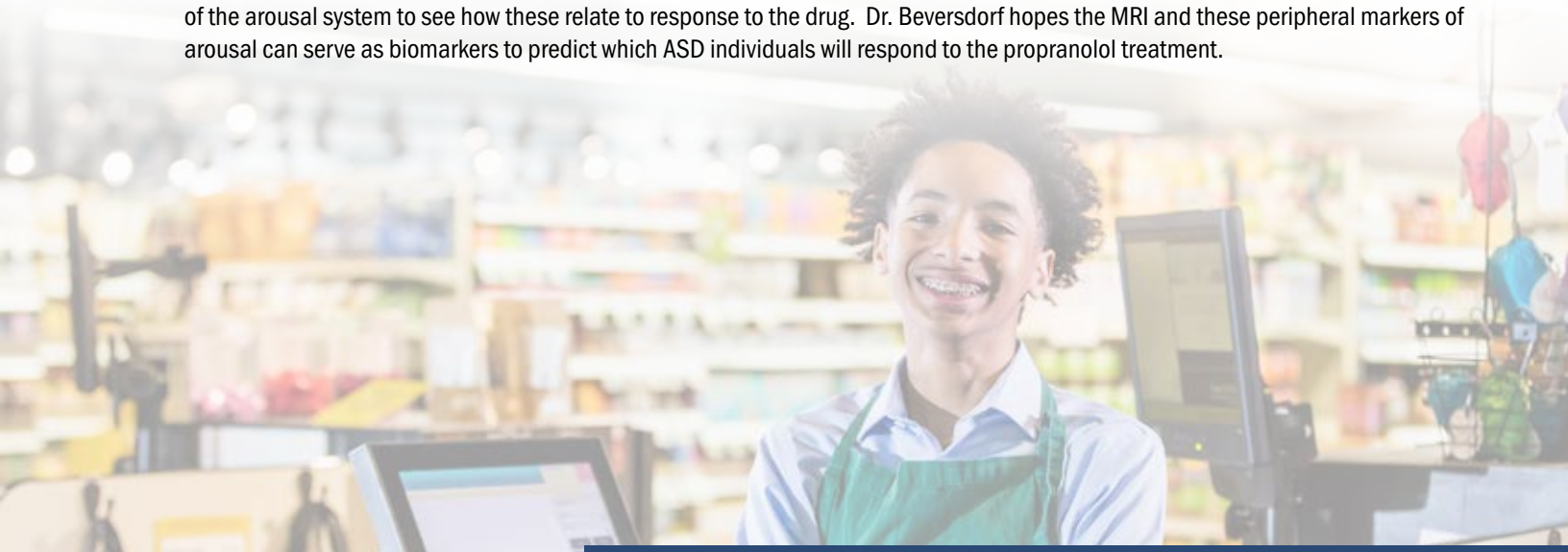
Raymond Booth, Ph.D., Northeastern University (shown left)
Clinton Canal, Ph.D., Mercer University (shown right)

Serotonin (5-HT) is a chemical that helps stabilize a person's mood and has been linked to ASD. The 5-HT1A and 5-HT7 receptors, in particular, are expressed in regions of the brain that control behaviors altered in ASD, and there is preclinical evidence that partial agonists to each receptor improves ASD symptoms. Drs. Raymond Booth and Clinton Canal postulated that targeting both receptors together may realize greater success. Drs. Booth and Canal were awarded a FY16 Idea Development Award to explore the development of novel drugs targeting serotonin receptors to treat ASD using mouse models. The team set out to design and synthesize compounds that target the 5-HT1A and 5-HT7 serotonin receptors. The team uncovered new compounds that attenuate repetitive behaviors in normal mice. One lead compound, 5-fluorophenyl-2-aminotetralin (FPT), modulated several behaviors in a genetic mouse model of ASD, including increasing social interactions, decreasing repetitive and anxiety-like behaviors, and preventing seizures caused by auditory stimuli. Furthermore, after FPT administration, c-Fos expression selectively increased in the amygdala of the autism mouse model, which might be a neural signal of reduced anxiety. These results demonstrate that the team has identified a compound that targets serotonin receptors and yields receptor activity that corrects the ASD core symptoms of repetitive behavior and impaired social interactions. The team will continue testing their lead compound as well as other top candidates in mouse models of ASD. They are on track to obtain an Investigational New Drug (IND) application, a request for authorization from the FDA to administer an investigational drug to humans.

Clinical Trial of Propranolol in Children and Youth with ASD

David Beversdorf, M.D., University of Missouri

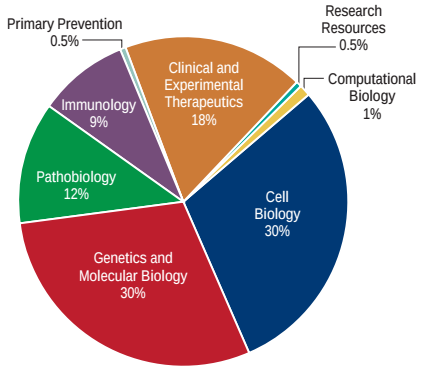
Propranolol is a drug commonly prescribed to lower heart rate, control blood pressure, and reduce anxiety. Due to the drug's ability to improve anxiety, Dr. David Beversdorf predicted that it would also improve social anxiety in individuals with ASD. In a single-dose propranolol pilot study, Dr. Beversdorf and his team found improvements in language and social interaction in individuals with ASD. With support from a FY15 ARP Clinical Trial Award, Dr. Beversdorf is now exploring the benefits of repeated doses of propranolol in adolescents and young adults with ASD. To date, the team has completed enrollment, and many participants have completed treatment. Another component of the ARP Clinical Trial Award is to understand the mechanism of propranolol on ASD. Dr. Beversdorf and his team are using magnetic resonance imaging (MRI) to identify brain activity patterns that are associated with the best response to the drug, as well as systemic markers of activity of the arousal system to see how these relate to response to the drug. Dr. Beversdorf hopes the MRI and these peripheral markers of arousal can serve as biomarkers to predict which ASD individuals will respond to the propranolol treatment.



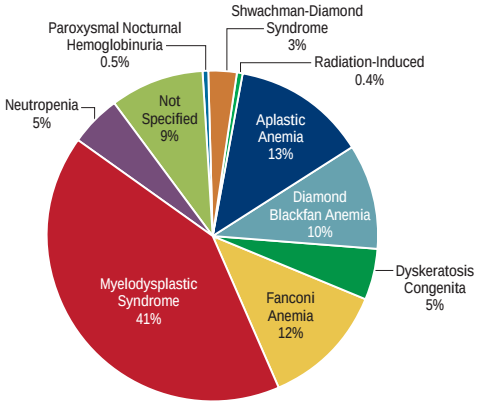
BONE MARROW FAILURE RESEARCH PROGRAM

Program History

The cavities of bones are made up of a spongy tissue that contains stem cells capable of maturing to blood cells in a process known as hematopoiesis. The hematopoietic cascade is responsible for the development of all cellular blood components, including red blood cells, white blood cells, and platelets. Disorders affecting the stem cells or progenitor cells can lead to bone marrow failure (BMF)—rare, potentially life-threatening diseases in which the bone marrow stops functioning or produces abnormal blood cells. These diseases can be either inherited or acquired. Inherited BMF includes a group of diseases where somatic genetic mutations lead to a deficiency in hematopoiesis that presents itself in childhood or early adulthood. Acquired BMF includes a group of diseases that can occur following an environmental exposure such as ionizing radiation, chemical contamination, or the long-term effects of chemotherapeutics. Both types of BMF lead to life-long chronic illnesses with the potential to develop cancer. The Peer Reviewed Bone Marrow Failure Research Program (BMFRP) was initiated in FY08 to provide support for exceptional innovative research focused on BMF diseases. From FY08 through FY19, $38.55M has been appropriated by Congress to research the prevention, causes, and treatment of BMF diseases. The appropriation for FY20 for the BMFRP is $3M. Thus far, the BMFRP has funded 77 awards, with the mission to support innovative research committed to advancing the understanding of inherited and acquired BMF diseases.



FY08-FY19 BMFRP Portfolio Investment by SCS Code*



FY08-FY19 BMFRP Portfolio Investment by Disease Classification*

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**

Examples of inherited BMF

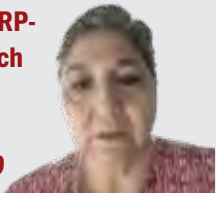
- **Fanconi anemia**
- **Dyskeratosis congenital**
- **Shwachman-Diamond syndrome**
- **Diamond-Blackfan anemia**
- **Inherited neutropenia**

Examples of acquired BMF

- **Aplastic anemia**
- **Myelodysplasia**
- **Paroxysmal nocturnal hemoglobinuria**
- **Pure red cell aplasia**

"I am a Severe Aplastic Anemia survivor enjoying my 11th anniversary on remission. It took the oncologist who first saw me a month and a battery of invasive exams to tell me the worst information: "I do not know what your disease is. Sorry, I cannot help you." Fortunately, he referred me to a team of researchers and within days, I received diagnosis and treatment with a combination of drugs that had been discovered through BMFRP-funded grants. Being able to aid in selecting the best research grants to be awarded has been one of the most rewarding experiences of my life."

Carmen Romo la Vivar, BMFRP Consumer Peer Reviewer FY19



*Percent Dollars Invested

Highlights

Understanding and Targeting How Mutant p53 Drives Clonal Hematopoiesis

Yan Liu, Ph.D., Indiana University, Indianapolis

Clonal hematopoiesis of indeterminate potential (CHIP) is a condition in which somatic mutations occur in hematopoietic stem and progenitor cells (HSPCs), giving rise to a genetically distinct blood lineage. Mutations in the tumor suppressor gene *TP53* can drive the expansion of HSPCs as one ages and increases the risk of blood-related cancers, including myelodysplastic syndromes (MDS) and acute myeloid leukemia, resulting in less than average clinical outcomes. *TP53* mutations are associated with short survival and drug resistance, thus constitute a critical area of research work. With a FY17 BMFRP Idea Development Award, Dr. Yan Liu sought to characterize the role of mutant p53 in the pathogenesis of MDS and identify novel therapeutic targets for MDS treatment. Using humanized knock-in mice, the team analyzed the peripheral blood and performed bone marrow transplantation assays. They observed an increased frequency of donor-derived HSPCs in the bone marrow of recipient mice–findings that suggest the expression of mutant p53 in normal hematopoietic stem cells (HSCs) does not cause leukemic transformation, but rather generates a premalignant state. This illustrates disease pathogenesis. Dr. Liu's team also discovered that HSCs with mutant p53 had a competitive advantage for cellular repopulation following transplantation and that mutant p53 promoted HSC expansion after genotoxic stress. They showed that the genetic and pharmacological inhibition of EZH2 (a functional part of a protein complex needed for HSC self-renewal and differentiation) reduces the repopulating potential of p53 mutant HSCs, indicating EZH2 as a novel therapeutic target in the prevention of CHIP progression and the treatment of hematological malignancies that are associated with *TP53* mutations.

Chen, S, Gao, R., Yao, C. et al. 2018. Genotoxic stresses promote clonal expansion of hematopoietic stem cells expressing mutant p53. *Leukemia* (32): 850–854

Chen, S., Yan, Q., Yu, S., et al. 2019. Mutant p53 drives clonal hematopoiesis through modulating epigenetic pathway. *Nat Commun* (10): 5649

Nabinger, S., Chen, S., Yao, C., et al., 2019. Mutant p53 enhances leukemia-initiating cell self-renewal to promote leukemia development. *Leukemia* (33):1535-1539

Macrophage-Mediated Hematopoietic Stem Cell Dysfunction in Severe Aplastic Anemia

Katherine MacNamara, Ph.D., Albany Medical College

Severe Aplastic Anemia (SAA) is a rare type of bone marrow disease that occurs when there is an extreme loss of HSCs, which can be lethal. Interferon gamma (IFNγ) has long been associated with SAA; however, its mechanism of action in relation to the disease is not fully understood. Through a FY16 BMFRP Idea Development Award, Dr. Katherine MacNamara utilized murine models of SAA to investigate the mechanistic role of IFNγ on HSC loss. Research conducted in this study showed that reduced macrophages or blocking IFNγ signaling in macrophages rescued the disease, but did not impair production of IFNγ in the mouse models, which suggested that macrophages act as key sensors of IFNγ in the disease process. Results show that IFNγ-dependent increase in bone marrow macrophages during SAA drives HSC loss and thrombocytopenia, creating a case for targeting macrophages and understanding how macrophages contribute to disease pathogenesis. Studies examined the efficacy of targeting two factors associated with IFNγ signaling in macrophages, the chemokine CCL5 and the protein podoplanin (PDPN), to improve SAA disease outcomes. The team showed that macrophages errantly express PDPN during SAA and that ligating PDPN to mimic receptor interaction improved HSC numbers and platelet output. Dr. MacNamara and her team believe that a deeper understanding of this macrophage-mediated process is crucial to the development of targeted therapy options for disease management.

McCabe A, Smith JNP, Costello A, et al. 2018. Hematopoietic stem cell loss and hematopoietic failure in severe aplastic anemia is driven by macrophages and aberrant podoplanin expression. *Haematologica* 103(9):1451-1461

"I was diagnosed with polycythemia vera in 1997 as a 21 year old and the disease was cured via stem cell transplant in 2013. Due in part to the advancements discovered/implemented by applicants and reviewers within the BMFRP program over the years, I had a much better outcome from my transplant than I likely would have had if I needed a transplant in 1997. My disease is cured and I only have very slight issues that resulted from the transplant. I am married and have an amazing 4-year-old daughter. It was a pleasure to serve as part of the panel in the hopes that these scientists and doctors can provide better outcomes for as many patients as possible in the future so others can be as fortunate as I have been."

Ed Russo, BMFRP Consumer Peer Reviewer, FY16, FY18, FY19

BREAST CANCER RESEARCH PROGRAM

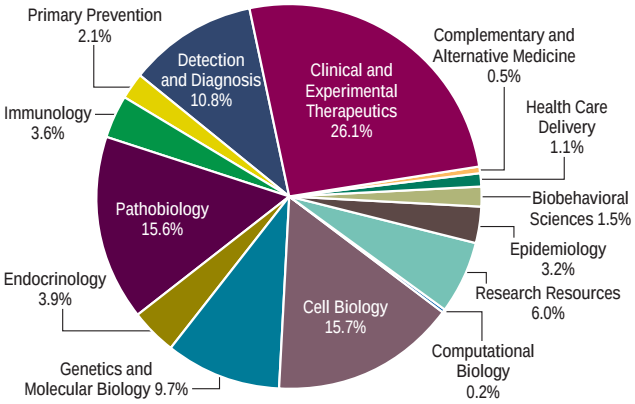
Vision: **A world without breast cancer**

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**

"With the collaborations of educated advocates and researchers, the DOD BCRP continues to fund high-risk, high-reward research that has resulted in the most significant scientific breakthroughs while bringing us closer to the end of breast cancer."
Michele Rakoff, Patient and Research Advocate

Program History

The DOD Peer Reviewed Breast Cancer Research Program (BCRP), established in 1992 as a result of breast cancer advocacy and congressional support, has received more than $3.7B in congressional appropriations through FY20. 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 the breast cancer research and patient communities. For example, preclinical research supported by the BCRP contributed to four FDA-approved drugs: trastuzumab, palbociclib, ribociclib, and abemaciclib.



FY92-FY19 BCRP Portfolio Investment by SCS Code

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:[1]

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

Breast Cancer Relevance to Military Health

Breast cancer causes the most cancer-related deaths in women under the age of 40.[2] Female active duty Service members have a 20%-40% higher incidence rate than the general public.[3] 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.[4]

Military Health System Data[5] (2007-2017):

- 104,498 incident cases of invasive breast cancer among female beneficiaries
- 23,013 incident cases of in situ breast cancer among female beneficiaries
- 861 incident cases of invasive breast cancer among male beneficiaries

New BCRP-Funded Clinical Trials Opened in 2020

HER2 Vaccine (TPIV100); Phase II (NCT04197687)

Keith Knutson, Ph.D., Saranya Chumsri, M.D., Mayo Clinic

This Phase II clinical trial will determine if boosting immune response with the HER2 vaccine, TPIV100, improves the efficacy of HER2-targeted therapy, trastuzumab emantasine (T-DM1), in HER2-positive breast cancer patients with residual disease after chemotherapy and surgery. The trial is also examining the safety of TPIV100 in patients with stage II and III disease who are at high risk for recurrence following neoadjuvant chemotherapy and surgical resection. Additionally, biomarkers of therapeutic success and failure will be evaluated in preparation for the planned follow-up Phase III trial at the conclusion of this study.

Neoadjuvant Endocrine Therapy (NET) + Radiotherapy: Phase I (NCT03804944)

Silvia Formenti, M.D., Sandra Demaria, M.D., Weill Medical College of Cornell University

This four-arm Phase II clinical trial is examining the safety and feasibility of combining the immunotherapeutics, Pembrolizumab and/or FMS-like tyrosine kinase 3 ligand (FLT3L; CDX-301), with traditional letrozole NET and focal radiotherapy in the neoadjuvant treatment setting. The trial will determine patient tolerability of each treatment regimen, clinical response rate, and pathological response rates in newly diagnosed post-menopausal women with stage II and III hormone receptor-positive breast cancer one month post-surgery.

Research Breakthroughs in Metastasis and Recurrence

Neutralization of BCL-2/XL Enhances the Cytotoxicity of T-DM1

Joan Brugge, Ph.D., Jason Zoeller, Ph.D., Harvard Medical School

An FDA-approved antibody-drug conjugate, T-DM1 has demonstrated clinical benefit in metastatic breast cancer; however, tumors ultimately become resistant. Two anti-apoptotic proteins, B-cell lymphoma 2 (BCL-2) and B-cell lymphoma extra-large (BCL-XL), were found to be upregulated in breast cancers and contribute to therapeutic resistance. With BCRP support, Dr. Brugge and Dr. Zoeller showed that a combination treatment of T-DM1 and the BCL-2/XL inhibitor ABT-263 in HER2-expressing metastatic patient-derived xenograft mouse models significantly enhanced tumor killing, which resulted in a reduction in tumor size and number of invasive tumors present. Administering ABT-263 in intervals, rather than continuously, demonstrated that toxic side effects associated with this inhibitor could be overcome without reducing pre-clinical effectiveness.

Zoeller JJ, Vagodny A, Taneja K, et al. 2019. Neutralization of BCL-2/XL enhances the cytotoxicity of T-DM1 in vivo. *Mol Cancer Ther.* 18(6):1115-1126.

Connecting Blood and Intratumoral Treg Cell Activity in Predicting Future Relapse in Breast Cancer

Peter Lee, M.D., Beckman Research Institute, City of Hope

Regulatory T (Treg) cells modulate the activity of tumor-killing effector immune cells and are implicated in the development of an immunosuppressive tumor microenvironment. Dr. Lee and his team developed a liquid biopsy-type metric that could be used to predict recurrence and monitor disease state based on the cytokine signaling index (CSI) of peripheral Treg cells. Peripheral Treg cells that were isolated from patients at diagnosis were found to be activated by immunosuppressive but not immunostimulatory cytokines. A high patient Treg response to immunosuppressive cytokines indicated a worse recurrence-free survival. Dr. Lee's team found that approximately 40% of patients with a CSI greater than the median patient CSI experienced recurrence at 36 months, while no patient with a CSI score below the median had detectable relapse. This early demonstration of a blood-based indicator for predicting recurrence is an exciting potential tool that is accurate and non-invasive.

Wang L, Simons DL, Lu X, et al. 2019. Connecting blood and intratumoral Treg cell activity in predicting future relapse in breast cancer. *Nature Immunology* 20(9):1220-1230.

[1] https://cdmrp.army.mil/bcrp/pdfs/Breast%20Cancer%20Landscape.pdf
[2] www.cdc.gov/cancers/dataviz
[3] Zhu K, Devesa SS, Wu H, et al. 2019. Cancer Incidence in the US Military Population: Comparison with Rates from the SEER Program. Cancer Epidemiol Biomarkers Prev 18(6): 1740-1745.
[4] Lee T, Williams VF, Taubman, SB, and Clark, LL. 2016. Incident diagnoses of cancers in the active component and cancer-related deaths in the active and reserve components, US Armed Forces, 2005–2014. MSMR 23(7): 23-31.
[5] Data provided by the Armed Forces Health Surveillance Branch Epidemiology & Analysis team based on records maintained in the Defense Medical Surveillance System

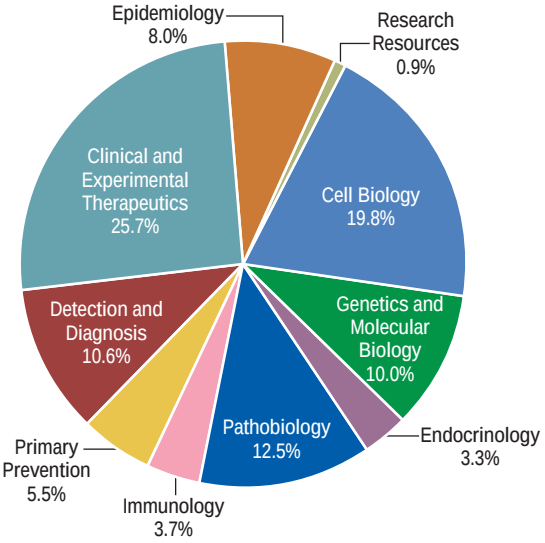
BREAST CANCER RESEARCH SEMIPOSTAL PROGRAM

Program History

As a result of the efforts of breast cancer advocates and congressional support, the Stamp Out Breast Cancer Act (Public Law 105-41) led to the US Postal Service's issuance of a new first-class stamp, the Breast Cancer Research Semipostal (BCRS) in 1998. It was the first semipostal in US history. Net revenues from sales of the BCRS, which currently costs 65 cents, are provided to two designated funding agencies, the DOD BCRP and NIH, to support breast cancer research. By law, 30% is allocated to the DOD BCRP, and 70% of the total amount raised is allocated to the NIH. The Breast Cancer Research Stamp Reauthorization Act of 2019 reauthorized the stamp through 2027.

Research and Management Costs

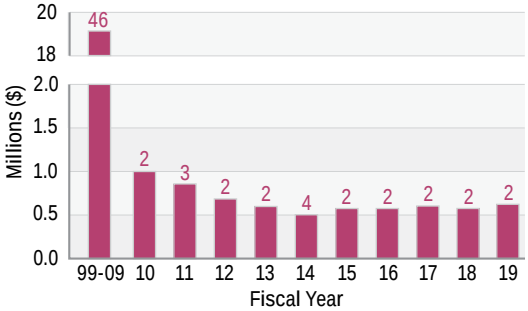
Breast cancer stamp funding received by the BCRP between FY99 and FY19 has been used to fully or partially fund 69 awards. These awards were funded under mechanisms that support innovative, high-risk, high-reward research that could lead to major advancements in breast cancer. Applications funded through the BCRS program were reviewed and recommended for funding according to the two-tier review system implemented by the DOD BCRP. An evaluation of the awards funded through the BCRS program shows that the projects encompass a diversity of research areas.



FY99-FY19 BCRS Portfolio Investment by SCS Code

Total Proceeds from BCRS (through FY19)	$26,479,234
Research	$25,196,496
Management Costs	$1,282,738

BCRS Research and Management Costs



BCRS Funding and Number of Awards

High-Impact Published Findings:

Strong mucosal immune programs were detected within lactating and involuting mammary glands in an animal model, which may inform the development or progression of postpartum breast cancer. (Dr. Pepper Schedin)

BRCA2 protein deficiency and associated DNA damage precede histologic abnormalities in vivo, offering opportunities for improved breast cancer risk assessment and prevention strategies. (Dr. Leif Ellisen)

Research Highlights

Lab-on-Chip (LOC) Platform for Assessment of Extracellular Matrix (ECM) Stiffness

Sophie Lelièvre, D.V.M., Ph.D., LL.M., Purdue University

The ECM provides structural support for cells in almost all organs in the body. Increased stiffness in the breast ECM has been associated with an increased risk in the development of breast cancer, suggesting that structural changes in the breast ECM play a role in cancer development. Because standard 2D cell culture models do not allow for accurate modeling of ECM stiffness, a variety of polymer-based hydrogels have been developed for use in 3D modeling techniques. Existing technologies for measuring ECM stiffness in these 3D models are typically either destructive or expensive, making them unsuitable for use in long-term small-scale applications, such as the LOC platform, used for measuring mechanical property changes in the microenvironment of cells in 3D culture. With BCRS support, Dr. Lelièvre and her team, including collaborator Dr. Rahim Rahimi, have developed a novel LOC platform that uses ultrasonic waves to quantify changes in ECM stiffness in real time. The device prototype has been developed, and initial cell viability assessments have been performed. Mammary stromal fibroblasts were embedded in 1.5% weight/volume agarose gel within the LOC and exposed to the ultrasonic wave signal over a 24-hour period. After 24 hours, there was no significant change observed in cell phenotype and no significant difference in the percentage of cells that underwent apoptosis, or cell death, compared to controls. Dr. Lelièvre and her team also demonstrated the capacity of the device to measure dynamic changes in stiffness of the 3D polymer in a non-destructive manner, while simultaneously allowing visualization of the cultured tissue. Since cells appear to remain viable in the LOC under continuous exposure to ultrasonic waves within the platform, the team hopes to use this technology to create a risk-on-a-chip platform that can be tailored to different risk factor(s) of interest, resulting in a personalized assessment of breast cancer risk, and to ultimately help clinicians identify potential prophylactic approaches for breast cancer patients. This novel platform also has implications for drug screening, providing a means of analyzing the impact different therapeutics have on tumor microenvironments and whether they have potential protective effects against breast cancer risk.

Zareei A, Jiang H, Chittiboyina S, et al. 2020. A lab-on-chip ultrasonic platform for real-time and nondestructive assessment of extracellular matrix stiffness. *Lab Chip* 20(4):778-788.

Targeting miR551b to Prevent Tumor Formation and Metastasis of Triple-Negative Breast Cancer (TNBC)

Pradeep Chaluvally-Raghavan, Ph.D., Medical College of Wisconsin

Evaluation of microRNAs offers a unique and unexplored strategy to examine subtype-specific mechanisms of metastasis and discover new therapeutic targets for treating breast cancer, including TNBC. Dr. Chaluvally-Raghavan's examination of microRNA551b-3p determined its role as a mediator of signaling addiction and metastatic activity via induction of an "oncostatin signaling module," which includes cytokines and their receptors that generate a persistent signaling loop through the well-known oncogenic transcription factor signal transducer and activator of transcription 3. Utilizing TNBC cell models and an animal model, the research team also demonstrated that disruption of this pathway via blocking microRNA511b-3p reduced migration and invasion activities (key features of metastasis), providing new opportunities for therapeutic approaches to treat TNBC and other cancers that employ this pathway in metastasis.

Parashar D, Geethadevi A, Aure MR, et al. 2019. miRNA551b-3p activates an oncostatin signaling module for the progression of triple-negative breast cancer. *Cell Reports* 29:4389-4406.

Recently Funded FY19 Awards

Targeting the Tumor Microenvironment and Metastatic Niche in Breast Cancer
Jeffrey Frost, Ph.D., University of Texas Health Science Center at Houston

A New Persistence Mechanism for Drug-Tolerant Breast Cancer Cells
Hannah Rabinowich, Ph.D., University of Pittsburgh

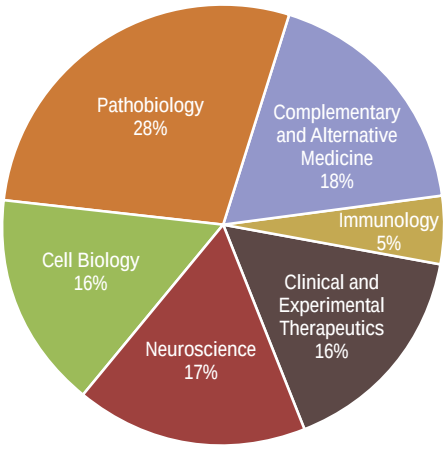
CHRONIC PAIN MANAGEMENT RESEARCH PROGRAM

Program History

The Chronic Pain Management Research Program (CPMRP) was established in FY19 with a congressional appropriation of $10M. Prior to this, chronic pain research had been supported by BAAs and other CDMRP programs, including the Defense Medical Research and Development Program, the Gulf War Illness Research Program, the Multiple Sclerosis Research Program, the Prostate Cancer Research Program, the Psychological Health/Traumatic Brain Injury Research Program, the Peer Reviewed Medical Research Program, the Peer Reviewed Orthopaedic Research Program, and the Spinal Cord Injury Research Program. From FY06 through FY18, the CDMRP has overseen an investment of over $174M in chronic pain research.

Per the 2011 IOM report, "Relieving Pain in America," over 100 million adults in the US suffer from chronic pain, of which 8 million report pain severe enough to interfere with daily living. A combination of health care costs and lost productivity results in an estimated total cost to the public of $600B per year from the effects of chronic pain. Following this report, the Interagency Pain Research Coordinating Committee and the NIH Office of Pain Policy created the Federal Pain Research Strategy, which identified gaps in pain research and highlighted cross-cutting themes and research priorities throughout the spectrum of pain, including chronic pain and the chronification of pain. These gaps and priorities provided a foundation for determining the CPMRP's role in chronic pain management research at its inaugural Stakeholders meeting.

On February 25, 2019, the CPMRP held a Stakeholders meeting, bringing together representatives from academic institutions, military installations, and national organizations including advocacy groups, who are invested in the management and treatment of chronic pain. A pre-meeting request for information identified topic areas that were explored by presentations from subject matter experts. Focused roundtable discussions were followed by group harmonization of priorities. A Programmatic Panel was established, comprised of expert clinicians, research scientists, and consumer advocates, who carefully considered the outcomes of the Stakeholders meeting to craft the Vision and Mission statements during the inaugural FY19 CPMRP Vision Setting. During Vision Setting, the panel members also distilled the research priorities identified at the Stakeholders meeting into Focus Areas, which were distributed in Program Announcements to solicit research of the highest needs and greatest impact for military Service members, Veterans, and all Americans currently managing or at risk of developing chronic pain. The FY19 CPMRP received 52 applications: 11 for Translational Research Awards and 41 for Investigator-Initiated Research Awards. Ultimately, the Programmatic Panel members recommended funding one Translational Research Award and five Investigator-Initiated Research Awards in FY19.



FY19 CPMRP Portfolio Investment by SCS Code

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

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

"The CDMRP is fostering the interdisciplinary investigation of the effects of non-pharmacologic approaches to managing pain. Pain is not only a prevalent issue for our military members and Veterans, it is a prevalent, disabling issue among the general population. As such, the effects of the panel's work to fund important research will reverberate throughout the nation."
Stephanie Taylor, Ph.D., M.P.H. FY20 CPMRP Programmatic Panel member; Associate Director, VA Center for the Study of Healthcare Innovation, Implementation, and Policy; VA Greater Los Angeles Healthcare System

FY20 Focus Areas

Focus Area	Specific Knowledge Gap
Chronification of pain (i.e., the transition of acute pain to chronic pain)	• Understanding mechanisms of, and developing models for studying, the transition from acute to chronic pain following trauma, either physical or psychological • Development of mechanistically justified therapies to prevent and treat chronification • Identification of risk or protection factors or biomarkers for patients susceptible to chronification, including relevant sub-populations
Development of novel non-μ-opioid receptor-targeted therapies for the treatment of chronic pain	• Novel non-opioid pharmacological solutions • Devices that treat chronic pain directly or those that improve the administration of non-opioid analgesics • Complementary and integrative health non-pharmacological interventions
Implementation science (for evidence-based, efficacious interventions to manage chronic pain)	• Unique barriers for delivery of complementary and integrative health therapies and models of care in military populations and environments, including at-risk sub-populations • Self-management and service-of-care models
Comparative effectiveness (for evidence-based, efficacious interventions to manage chronic pain)	• Multimodal and combination therapies • Pain and its bi-directional interactions with co-morbidities (e.g., polytrauma triad, suicidal thoughts and behaviors, substance abuse, etc.)

FY20 Award Mechanisms

Translational Research Award

The FY20 CPMRP Translational Research Award intends to support translational research that will accelerate the movement of evidence-based ideas in chronic pain management research into clinical applications, including healthcare products, technologies, practice guidelines, and/or models of care. This mechanism will support the Focus Areas of Implementation science and Comparative effectiveness, encouraging the advancement of interventions with known efficacy. Effectiveness-implementation hybrid type 2 and type 3 studies are also encouraged. All Comparative effectiveness and Effectiveness-implementation hybrid studies should incorporate a biopsychosocial model of pain assessment that includes pain interference in emotional and physical functioning.

Investigator-Initiated Research Award

The FY20 CPMRP Investigator-Initiated Research Award intends to support basic through clinically oriented investigations, but not clinical trials, that have the potential to make an important contribution to research, patient care, and/or quality of life. This mechanism will support the Focus Areas of Chronification of pain and Development of non-μ-opioid receptor-targeted therapies for the treatment of chronic pain. Multidisciplinary collaborations and innovative approaches are highly encouraged to gain knowledge about the transition of acute to chronic pain and to develop treatments for chronic pain.

For all FY20 CPMRP award mechanisms, the incorporation of pain informatics; pragmatic approaches; patient expectations, preference, and goals of treatment at point of care; multiple ecological levels and stakeholder engagement in studies designs with human participants; chronic pain conditions with high prevalence in military populations; and established models of pain assessment that include pain interference in emotion and physical functioning in research approaches is encouraged.

"Chronic pain is one of the costliest and most disabling conditions in the United States and represents a significant problem for US active duty Service members and Veterans. The CDMRP has played a significant role in research addressing chronic pain over the past several decades, and this outstanding work has culminated in a research program now specifically focused on addressing this major concern. The Chronic Pain Management Research Program represents the CDMRP's commitment to science that will deepen our understanding of chronic pain and sharpen our ability to treat it."

Donald McGeary, Ph.D., ABPP, FY20 CPMRP Programmatic Panel Chair; Associate Professor, University of Texas Health Science Center at San Antonio

COMBAT READINESS-MEDICAL RESEARCH PROGRAM

Program History

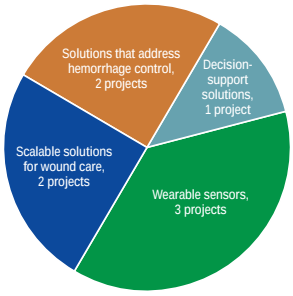
The Combat Readiness – Medical Research Program (CRRP) was established in FY19 to pursue military-relevant advanced technology and therapeutic research related to forward-deployable solutions that can promptly address life-threatening injuries, medical threats, and treatments for Service members in battlefield settings. From FY19 through FY20, CRRP received $25M in congressional appropriations. The congressional language for the CRRP encompasses research that would enable the Warfighter to better respond to serious injury and mitigate the long-term effects of battlefield trauma in rural and austere environments, as well as solutions that can translate to prolonged prehospital civilian trauma care in situations of mass casualty events and/or extended disrupted communications in dense urban or subterranean environments. Synergistic topics related to medical combat readiness research have been supported by the DHP Core and other Congressional Special Interest programs that are managed by CDMRP. CRRP included representatives from these programs in its inaugural Programmatic Review to ensure funding efforts were not duplicative and the program was meeting an unmet need that synergistically aligned with directives from Congress.

FY20 Award Mechanism

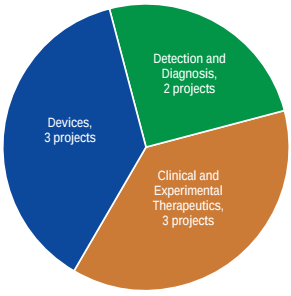
Rapid Development and Translational Research Award

The intent of the FY20 CRRP Rapid Development and Translational Research Award is to support high-impact research that will accelerate the movement of promising ideas into clinical applications, including military-relevant healthcare products, technologies, and/or practice guidelines to deliver life-saving care to the Warfighter during prolonged and en route care in austere and combat environments. The program seeks projects which consider the varied expertise levels of the medical providers and the possible diverse environmental conditions in combat theater, characteristics relevant to military use in non-hospital settings in theater, and solutions which can translate to advancements in civilian trauma care. This mechanism will support all CRRP Focus Areas.

Portfolio Composition



FY19 CRRP Investment by Focus Area (Plotted by Number of Awards)



FY19 CRRP Portfolio Investment by SCS Code (Plotted by Number of Awards)

"Serving on the CRRP Programmatic Panel is an opportunity to collaborate and work synergistically with other government programs and stakeholders to accelerate innovative medical advances to our Warfighters on the battlefield. [The JPCs] are able to maximize the available funds to support the missions of the DHA's JPCs, including the CCCRP."

Therese West DNP, APN-BC, Combat Casualty Care Research Program (CCCRP), FY20 CRRP Programmatic Panel Member

Vision: **Deliver high-impact medical solutions throughout the continuum of care to increase survivability and readiness of the Warfighter in diverse operational settings**

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

"The Goal of the CRRP is to support and fund combat and deployment related research with military and civilian scientists, clinical investigators, and field operators to deliver solutions, innovations, knowledge products, and material solutions for the combat medic to improve the survival and return to duty rates of the warfighter for the future battlefield. We aim to improve the care of combat related injury and illness..."

Vikhyat Bebarta, University of Colorado, Denver; FY19 and FY20 CRRP Programmatic Panel Chair

FY20 Focus Areas

- Multiple-use scalable wound-care solutions that can address prevention of bleeding and infection, delivery of therapeutics, and promotion of healing spanning acute through chronic care
- Repair and/or restoration of combat-related genitourinary organ and tissue damage
- Solutions for assessment of mTBI in deployed and far forward settings to include portable devices
- Research and development of freeze-dried plasma and platelets to address hemorrhage and resuscitation
- Solutions to enhance Warfighter readiness in battlefield and austere environments including the prevention and treatment of
  - GI illness such as Enterotoxigenic Escherichia coli diarrheal disease and inflammatory bowel disease
  - Sleep disorders
  - Myalgic encephalomyelitis/chronic fatigue syndrome
  - Infectious diseases
- Enhanced delivery and utilization of telemedicine platforms

Highlights

In its inaugural year, the FY19 CRRP received 168 compliant proposals and recommended funding 8 Rapid Development and Translational Research Awards. The projects below represent some of the promising research supported by the CRRP.

A Field-Deployable Dielectric Coagulometer for Point-of-Care Assessment of Trauma-Induced Coagulopathy

Michael Suster, Ph.D., Case Western Reserve University

Trauma-induced coagulopathy (TIC), failure of the blood to clot following trauma, is a significant cause of excessive bleeding, ongoing hemorrhage, and post-traumatic death both on and off the battlefield. Dr. Michael Suster and team at Case Western Reserve University have developed ClotChip,™ a microfluidic sensor that provides rapid assessment of a patient's bleeding risk profile. In collaboration with XaTek, Inc., which has developed a portable, handheld ClotChip system for use in civilian markets, the team plans to leverage the ClotChip technology for the development of a ruggedized prototype with increased durability for use in military operational environments. The efficacy of the ClotChip system will first be validated in an animal model of TIC at Naval Medical Center Portsmouth (NMCP) and then tested for field use at NMCP. This research addresses two FY19 Focus Areas: (1) solutions that address hemorrhage control and (2) decision-support solutions for triage and management of severely injured Warfighters. Deployment of this technology will inform personalized treatment procedures following injury for more efficient and effective use of critically limited blood supplies and will ultimately reduce the number of combat casualties.

Combat-Ready Exposure Device (CRED): Validation of a Portable Exposure Biomarker Device for Lead and Other Heavy Metal Exposures

Susan Proctor, D.Sc., US Army Research Institute of Environmental Medicine

Exposures to toxic levels of heavy metals can have immediate and long-term neurological and physical impacts. For military personnel, heavy metal exposures are of particular concern due to repeated acute and/or chronic exposures that may come from multiple sources in combat, including burn pits, ammunition and munitions, and particulate matter from improvised explosive devices. Current methods for detecting heavy metals exposure require specialized medical professionals and large stationary equipment, and there is a need for fieldable materiel capabilities within the DOD. Addressing the FY19 Focus Area of wearable sensors, Dr. Susan Proctor and team proposed to refine and validate a portable, CRED that uses X-ray generators and energy detectors for the detection of lead and other heavy metals (i.e., mercury, manganese, copper, and tungsten) in human blood and tissues. The proposed prototype will combine validated metrics for human-absorbed heavy metal dose with portability for monitoring both acute and chronic heavy metal exposures in field settings. With applicability in forward operational combat environments, as well as civilian and military higher echelon clinical care settings, the CRED prototype is a necessary first step to develop a wearable sensor to detect and monitor the body burden to heavy metals exposures. A device such as this one will not only have an immediate impact on informing treatments at the point of exposure, but can also provide insight into the long-term health risks associated with exposure to heavy metals.

DUCHENNE MUSCULAR DYSTROPHY RESEARCH PROGRAM

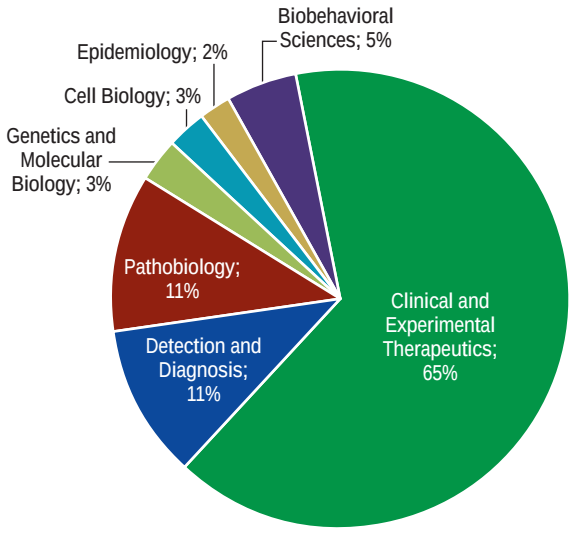
Program History

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

The Peer Reviewed Duchenne Muscular Dystrophy Research Program (DMDRP) was established in FY11 and has received $39.6M in congressional appropriations through FY20. The DMDRP has a research portfolio of 37 projects that include studies on the cardiac issues associated with DMD, research to improve clinical care and quality of life, assessment of clinical trial tools and outcome measures, and preclinical translational research to support therapeutic development. There is no treatment that can stop or reverse the progression of DMD. With the lack of any curative treatments, the DMDRP has placed its greatest emphasis on developing or improving treatments and clinical trial readiness.

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

Mission: **To better support discovery and development of therapeutics, devices, and other interventions, and to promote their rigorous clinical testing for the benefit of military beneficiaries and the general public**



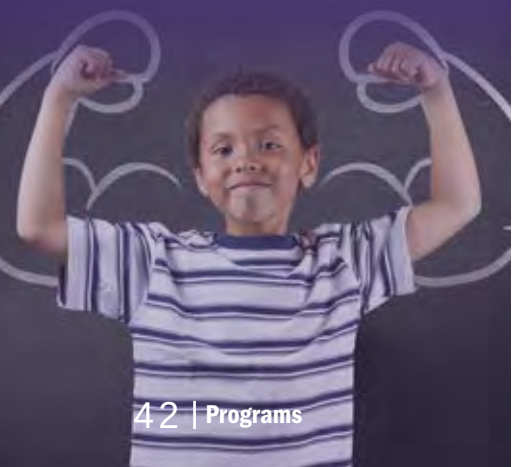
FY11-FY19 DMDRP Portfolio Investment by SCS Code

Products Advancing Towards the Market

- **Vamorolone, a novel anti-inflammatory drug with fewer metabolic side effects than corticosteriods is in phase 2b clinical trial testing in steriod naïve boys with DMD**

"I have been honored to serve on the Department of Defense DMDRP programmatic review committee for 4 years. The DMDRP is unique in that the grants funded by the program aim to address the needs of the Duchenne community, including military families. The DMDRP commitment to improving the function and quality of life of all individuals with DMD, allows Service members with children affected by DMD to maintain their military focus and be mission ready, while continuing the fight against DMD."

Maj Michele Gatheridge, Programmatic Panel Member, San Antonio Military Medical Center



Preclinical Research Translating to the Clinic

Accelerate promising therapeutics into clinical applications:

- Independent studies by Drs. Dongsheng Duan and Barry Byrne on vector optimization, production, and delivery methods for gene therapy have led to a clinical trial evaluating μ-dys gene transfer (SGT-001) in adolescents and children with DMD (NCT03368742)
- Dr. Rita Perlingeiro is optimizing production of clinical-grade pluripotent-derived myogenic progenitors for therapeutic application in DMD

Assess clinical trial tools and outcome measures:

- Dr. Yetrib Hathout identified and validated pharmacodynamic serum biomarkers for monitoring disease progression and treatment
- Functional assessments of upper body movement using a "novel video game based approach" by Dr. Linda Lowe have shown correlation with standard walking test outcome measures

Assess Duchenne's effect on bone, heart, central nervous system, and the GI tract:

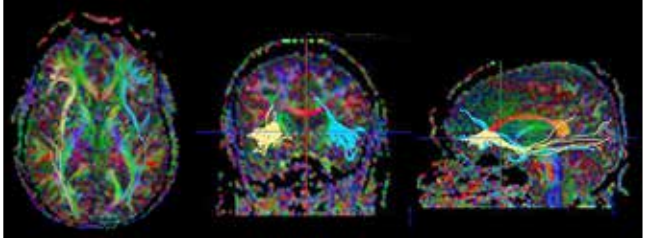
- Research by Dr. Kathleen Rodgers has developed a Mas agonist drug to reduce DMD cardiomyopathy and currently her team is evaluating the safety and efficacy of MMX1902 in combination with ACE and ARB inhibitors
- Dr. Dongshen Duan and Dr. Charles Gersbach are collaborating to use gene editing via CRISPR/Cas9 to restore dystrophin expression in the heart and study its safety

Improve clinical care and quality of life:

- Supporting research by Dr. Tanja Taivassalo studying the interplay of a low-dose corticosteroid weekend regimen and exercise training
- Dr. Andres Barth is assessing arrhythmic risk in adult patients with DMD and whether there is an increased frequency of ventricular arrhythmias that correlate with sudden death observed in these patients

"I have been in the Duchenne muscular dystrophy research space for over 20 years now, working for both large and small non-profit organizations and companies and have served on advisory councils for government entities. The CDMRP funding process is a truly unique and thoughtful way to make funding decisions, taking into account both scientific aspects and the context of the project. The DMDRP has had a significant impact already in translating promising technologies like gene therapy into trials for Duchenne, and I'm very enthusiastic about the vision and projects that have been identified through the process this year. This should be a diagnosis that no parent should have to fear."

Sharon Hesterlee, Ph.D., Programmatic Panel Member, Muscular Dystrophy Association



EPILEPSY RESEARCH PROGRAM

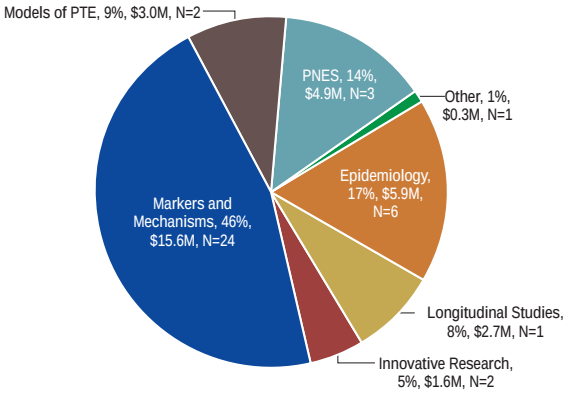
Program History

The DOD Peer Reviewed Epilepsy Research Program (ERP) was established in FY15 in response to concerns about the long-term consequences of TBIs. The ERP aims to understand the basic mechanisms by which TBI produces PTE and the extent of PTE following TBI within the military. Mild, moderate, and severe TBI have been linked to epilepsy; however, the mechanisms underlying this relationship remain unknown. The ERP has funded 39 research projects since its inception in FY15, which examine a wide range of topics, including new and innovative animal models, differences between PTE and psychogenic non-epileptic seizures, functional brain changes associated with PTE, and epidemiological studies of Service members.

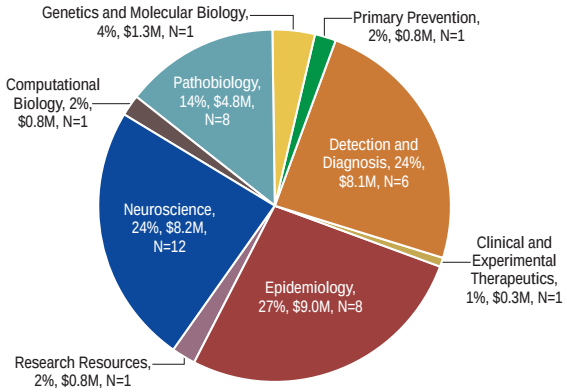
Focus Areas

The ERP offers award mechanisms with the intent to solicit innovative and impactful research in PTE. The program has the following Focus Areas that will help researchers address the ERP's Mission and Vision:

- **Innovative Research:** Tools intended to better inform or improve how PTE research can be performed
- **Markers and Mechanisms:** Identifying markers or mechanisms via preclinical models that address PTE
- **Epidemiology:** Epidemiological characterization of PTE following TBI
- **Longitudinal Studies:** Studies of the evolution of PTE
- **Quality of Life:** Improving quality of life of individuals with PTE and their caregivers



FY15-FY19 ERP Portfolio Investment by Focus Area



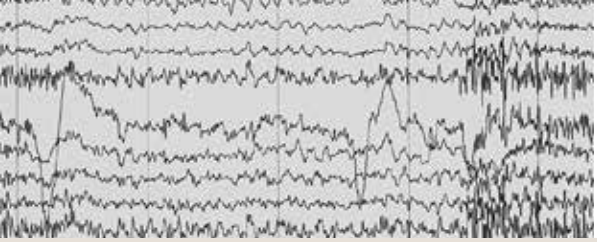
FY15-FY19 ERP Portfolio Investment by SCS Code

Vision: **A time when the causative links between TBI and epilepsy are understood and PTE is both preventable and treatable**

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

"The ERP funds high-risk, high-reward research that is providing insights on how traumatic brain injury can result in PTE as well as who may be most at risk for developing PTE. The ERP also funds critical research on other types of epilepsy that can have a profound impact on our Service members, Veterans, and civilians. As a programmatic review panel member, I am excited to see the advancements that have already been achieved…and am eager to see how it will improve the quality of life all those affected by epilepsy."

Laura Lubbers, Chief Scientific Officer, Citizens United for Research in Epilepsy



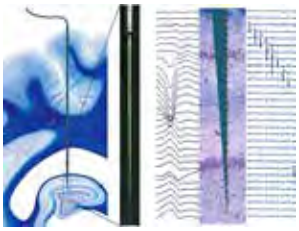
Research Highlights

Large Animal Models of TBI May Reveal the Mechanisms Behind Post-Traumatic Epilepsy

John A. Wolf, Ph.D., University of Pennsylvania

Many Service members and civilians who suffer a TBI later develop spontaneous recurrent seizures (i.e., PTE). During the time between the TBI and the development of PTE, the brain undergoes changes that make it prone to seizures, a process known as epileptogenesis. The mechanisms of epileptogenesis are not fully understood, and predictors (biomarkers) of who will go on to develop PTE following a TBI are not well established. Both of these questions, how to intervene and on which TBI patients to deploy an intervention, are the goals of a new study.

Dr. John Wolf, of the University of Pennsylvania and the Philadelphia CMC VA Medical Center, is using a large animal (pig) model to break new ground in PTE research. This model of PTE approximates the human brain better than a rodent model and allows Dr. Wolf to measure the degree to which different injury types contribute to the development of epilepsy. He has also carefully characterized the extent of the injuries to these animals in an effort to understand which brain structures are most susceptible to damage from a head injury, as well as which regions might become hyperexcitable or dysfunctional leading to acquired epilepsy. In addition, measurements from the blood are being taken in order to predict which animals will go on to develop epilepsy in hopes of using this information to make better predictions for patients.



Histological characterization of the dorsal hippocampus of Yucatan miniature pigs. Stereotaxis combined with single-unit electrophysiological mapping was used to precisely place multichannel laminar silicon probes into the dorsal hippocampus without the need for image guidance. In vivo electrophysiological recordings of simultaneous laminar field potentials and single-unit activity in multiple layers of the dorsal hippocampus were used to physiologically identify and quantify these layers under anesthesia.

Another major challenge that Dr. Wolf is addressing is how to measure alterations in brain activity after injury over long periods of time, which has never been done previously in a large animal model. Dr. Wolf and his team designed an integrated system that can measure the spread of abnormal electrical activity in the brain after injury, including in deep brain structures with high resolution. The preliminary data generated by this work has already led to a greater understanding of how early post-injury dysfunctional activity occurs. Dr. Wolf is preparing to generate maps of how adjacent regions of the brain alter their communication after injury. Understanding the start and spread of these network disruptions will reveal novel mechanisms related to epileptogenesis and may lead to advances in seizure detection, as these experiments may reveal the earliest events and locations involved in PTE. A better understanding of the mechanisms of epileptogenesis should allow for more targeted treatments, with the goal of blocking the development of epilepsy following TBI.

The Epidemiology of Epilepsy and Traumatic Brain Injury: Severity, Mechanism, and Outcomes

Mary Jo Pugh, Ph.D., RN, South Texas Veterans Health Care System

The roadmap toward designing the next generation of clinical trials for PTE is complex. While many pharmacological treatments are available, they are not always effective and can have side effects that seriously affect daily living. A key and critical facet of moving clinical interventions forward is understanding who is most vulnerable to PTE following a TBI. Only after identifying that group of individuals can a careful assessment of their needs and challenges be ascertained.

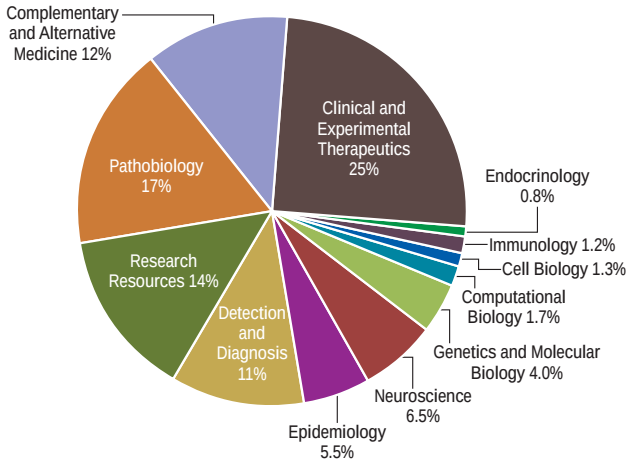
Dr. Mary Jo Pugh has begun asking these essential questions and has taken up the challenge of characterizing PTE among Veterans. Basic questions like, "how many post-9/11 Veterans have epilepsy or have had a TBI?" remain unanswered. Finding the answers to these questions will help us understand the interrelationship between TBI and epilepsy, as well as what accelerates or increases vulnerability to epilepsy after TBI. Dr. Pugh hypothesized that co-morbidities, such as mental health issues, may be present in individuals with PTE and inhibit their ability to function independently. To date, she has started to measure the behavioral and cognitive consequences of TBI in individuals with TBI/epilepsy. She has found that individuals with both conditions may face worse consequences, such as depression, suicidality, and self-reported memory problems. Her preliminary data also suggests that women with both TBI history and epilepsy are more vulnerable to these and other outcomes such as self-reported quality of life.

When the study is completed, an improved understanding will be gained of who is most vulnerable and how their daily lives are affected. In addition to informing the types of medications they should receive, studies such as these may aid in further tailoring their care. For example, individuals facing mental health issues may receive increased psychological counselling to help them deal with this co-morbidity, and those reporting memory problems may be followed more closely to assess the possible emergence of cognitive disorders.

GULF WAR ILLNESS RESEARCH PROGRAM

Program History

The Peer Reviewed Gulf War Illness Research Program (GWIRP) was established in 2006 and renewed by Congress in 2008 to support research focused on improving treatments for GWI. Prior DOD-funded research into GWI was managed by the USAMRDC Military Operational Medicine Research Program or intermittently through CDMRP. Since FY06, the GWIRP has received a total of $214M in congressional appropriations, including $22M in FY20. From these appropriations, the program has built a broad research portfolio of over 160 projects that include clinical trials, mechanistic research, and studies addressing chemical exposures and GWI symptomatology. The program continues to support innovative, competitively peer-reviewed research to develop treatments addressing the complex symptoms that comprise GWI and its underlying causes, to identify objective markers (biomarkers) improving its diagnosis, and to better understand the pathobiology underlying GWI. Multi-institutional research consortia have proven to be an effective mechanism for fostering collaboration and rapid communication of research findings between investigators in all phases of research.



FY06, FY08-FY19 GWIRP Portfolio Investment by SCS Code

Overarching Challenges

Considering the current GWI Landscape and the GWIRP's mission, the FY20 applications must address at least one of the following overarching challenges:

- Treatments: Eliminate the health consequences associated with GWI and revolutionize treatment
- Diagnosis: Better define and diagnose GWI
- Subtyping: Distinguish symptom clusters to better target treatments, identify underlying causes, and elucidate differences in severity
- Determinants: Validate exposures associated with GWI and impacts on organs and systems
- Consequences: Determine whether GWI is associated with greater risk for developing other disease states, including neurological diseases, cancers, or other life-threatening and severely debilitating conditions
- Communication: Help Veterans, their caregivers, researchers, and health care providers communicate effectively about GWI, its symptoms, and potential treatments

Vision: **Improve the health and lives of Veterans who have Gulf War Illness**

Mission: **Fund innovative Gulf War Illness research to identify effective treatments, improve definition and diagnosis, and better understand pathobiology and symptoms of disease**

"I'm grateful for the members of Congress that have stood by Gulf War Veterans, support which has never wavered. I'm grateful for the leadership within the Department of Defense that helps to make this program happen and helps to ensure that this program is indeed finding and funding the best research aimed at finding treatments and cures for Gulf War Illness."
Anthony Hardie, GWIRP Programmatic Panel member, Programmatic Panel Chair Emeritus and Consumer; Veterans for Common Sense

Research Highlights

Alleviating Headache and Pain in GWI and Neuronavigation-Guided rTMS

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

Headache and pain are some of the most common debilitating symptoms in Veterans with GWI and have a significant impact on quality of life. Conventional pharmacological treatments for these symptoms have proven ineffective and often result in a number of negative side effects. Previous research has shown that non-invasive brain stimulation such as repetitive Transcranial Magnetic Stimulation (rTMS) can ameliorate the symptoms of a number of chronic pain conditions and headaches when applied to specific regions of the brain. With funding from a FY15 GWIRP Innovative Treatment Evaluation Award (ITEA), Dr. Albert Leung conducted a pilot randomized, controlled clinical trial to validate one of these case reviews from a small group of Gulf War Veterans that suggested improvements in headache following treatment with rTMS.

The GWIRP ITEA study examined 40 Gulf War Veterans with GWI and 20 healthy Gulf War Veteran controls from the VA San Diego Healthcare System and Naval Medical Center San Diego. Veterans were given four rTMS or sham treatments over a period of 1 week and were assessed during treatment and at 1, 4, and 8 weeks post-treatment. Headache patterns and joint and muscle pain were assessed in each group using a daily headache and pain diary. A comparison of the Gulf War Veterans who received rTMS to those in the sham group demonstrated that rTMS treatment resulted in significant improvements in muscle pain as well as in concentration and fatigue. Improvements in headache and joint pain also trended toward significance. Veterans with chronic pain required significantly higher levels of stimulation to evoke motor responses compared to control subjects. Additionally, Veterans with chronic pain were found to have diminished corticomotor excitability, providing new insight into the neuromodulatory functions underlying GWI.

The results of this pilot study provided the foundation to design and conduct larger-scale, multi-center treatment trials of rTMS. In FY18, VA Clinical Science Research & Development funded a multi-center, four-arm study to access rTMS in Gulf War veterans with GWI. Dr. Leung also received additional funding from a GWIRP Clinical Trial Award for a complementary multi-center, two-arm clinical trial to address a sub-population, meeting the GWI diagnostic headache and pain criteria, but with different severities of comorbid symptoms than those addressed in the VA funded trial. The two funding mechanisms, which will work synergistically to advance the intervention, could provide a new treatment option for Gulf War Veterans living with GWI-related headaches and chronic pain and ultimately improve their quality of life.

Prevalence and Patterns of Symptoms Among Female Gulf War Veterans

Steve Coughlin, Ph.D., M.P.H., Augusta University

Kimberly Sullivan, Ph.D., Boston University School of Public Health

Women comprised 7% of the nearly 700,000 military personnel who served in the 1990–1991 Gulf War.

In 2015-2016, the Veterans Affairs Cooperative Studies Program conducted the Gulf War Era Cohort and Biorepository study, which tallied questionnaire responses from 1,318 Gulf War-deployed and Gulf War-era Veterans concerning their health status and symptoms. Dr. Steven Coughlin at Augusta University and a team of GWI researchers, including Dr. Kimberly Sullivan at Boston University, are using an FY15 GWIRP Gulf War Illness Epidemiology Research Award to probe the results of this survey as they relate to female Veterans' health issues. The study aimed to examine the frequency and patterns of health symptoms 25 years post-deployment in Gulf War-deployed and Gulf War-era women Veterans from all military branches. It was hypothesized that symptoms associated with the diagnostic pattern of GWI, including fatigue, chronic pain, and cognitive complaints, would be higher in female Gulf War Veterans. A total of 301 women Veteran responses were analyzed in the study.

The results indicate that women Veterans from all branches of the military who were deployed to the Gulf War continued to report a wide variety of symptoms at a higher frequency than other Gulf War-era women Veterans. The significantly different excess symptoms related to cognitive and mood problems and respiratory complaints aligned with symptoms from the CDC and Kansas case criteria.

Dr. Sullivan's article also highlighted associations between deployment status and respiratory symptoms, cognitive symptoms, and psychiatric symptoms. The high symptom burden observed in this study, leading to diminished quality of life, is likely to at least partly account for psychiatric symptoms such as depression and anxiety.

There were limitations, since participation was elective, leading to potential selection bias. Information about symptoms was self-reported and no distinction was made about exposures during deployment, which could under-report symptom burden in exposed groups.

These findings contribute to the knowledge base seeking to develop biological markers of GWI and effective treatments for this debilitating condition which may be gender specific.

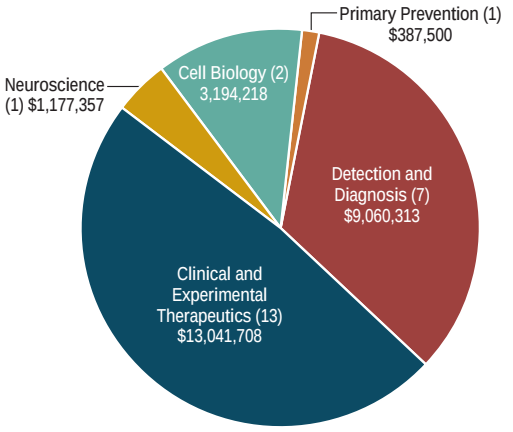
HEARING RESTORATION RESEARCH PROGRAM

Vision: **Improve the operational performance, 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

The Peer Reviewed Hearing Restoration Research Program (HRRP) was initiated in 2017 to support innovative and impactful research that pursues the treatment of auditory system injuries and the restoration of hearing. Appropriations for the HRRP from FY17 through FY19 totaled $30.0M. Research supported by the HRRP focuses on the development and translation of hearing restoration therapeutics, including innovative diagnostics to facilitate clinical testing, and the advancement of acute auditory system injury diagnosis in the military operational environment.



FY17-FY19 HRRP Portfolio Investment by SCS Code (Number of Awards)

Relevance to Military Health

Service members face high risks of noise-induced hearing loss and auditory system injury, including the potential for hidden hearing loss (e.g., cochlear synaptopathy). Service members are exposed to high levels of noise (e.g., gunshots, helicopters, explosions, aircraft take-offs from carrier deck, etc.) unique to military operating and training environments. In contrast with exposure to noise in construction, agriculture, and recreation, encountering combat noise is not predictable, and protection against combat noise is further complicated by the need for Warfighters to hear sound and to communicate. Furthermore, Service members often operate in austere/remote environments without access to a fixed or mobile medical facility and where diagnostic and treatment resources and medical personnel are unavailable or limited for extended periods of time. Data from the VA Veterans Benefits Administration indicate that the two most prevalent service-connected disabilities are related to hearing disorders, with more than 1.1 million Veterans suffering from hearing loss.

Focus Areas

- Accelerate translation of biological regeneration/repair mechanisms into therapies that treat auditory system injury and restore auditory function
- Diagnostic tests that help differentiate sensory, neural, synaptic, and central processing disorders, that may inform applicability and outcomes for current or future hearing restoration therapeutics
- Develop reliable in-vitro human models to facilitate the understanding, derivation, and characterization of human auditory cells, and/or to facilitate the evaluation of hearing restoration therapies
- Develop and/or validate techniques/methods beyond the audiogram to diagnose acute auditory system injury in austere or remote environments. For example, but not limited to, simple and rapid assessments that are compatible with portable platform

Research Highlights

Miniature Intracochlear Imaging Probe Based on Micro Optical Coherence Tomography for Cellular-Level Diagnosis and Therapy of Hearing Loss

Konstantina Stankovic, M.D, Ph.D., Massachusetts Eye and Ear Infirmary

Sensorineural hearing loss (SNHL) affects 466 million individuals worldwide and is one of the most common war-induced injuries among American military personnel. Efforts to understand, diagnose, and develop treatment for SNHL are severely hindered by a lack of ability to examine cochlear pathology at the cellular level. Dr. Stankovic's team has previously shown that micro-optical coherence tomography (micro-OCT), a 1-micrometer-resolution successor to standard clinical OCT, can resolve intracochlear cells and auditory nerve fibers and reveal cochlear microstructure. With support from an HRRP FY19 Focused Research Award, Dr. Stankovic hopes to make a breakthrough in the diagnosis of cellular-level cochlear pathology by developing and optimizing a micro-OCT imaging probe and system within a sub-milimeter-diameter probe for microendoscopy. Furthermore, the team will integrate the probe with a cochlear implant (CI) electrode array to enable next-generation CIs with superior safety and efficacy. Successful completion of this project will produce a clinical-grade, high-resolution intracochlear micro-OCT probe and system ready for clinical trial, revolutionizing the diagnosis and treatment of SNHL.

Towards a Self-Administered Hearing Protection Regimen

Donna Whitlon, Ph.D., Northwestern University

Hearing is dependent on the integrity of multiple cellular, biochemical, and neural pathways in the cochlea and the brain. Currently there are no drugs that are FDA approved to prevent or repair hearing loss of any etiology. Dr. Whitlon envisions that broadly applicable treatments may be found by targeting molecular pathways that are common to various auditory insults. Preliminary studies from her lab suggested that statins, a class of readily available drugs commonly used to treat high cholesterol, are protective against hearing threshold increases and cochlear structure damage in two animal models. The team recently received an HRRP FY19 Focused Research Award to further investigate statins as promising drugs to treat hearing loss. Specifically, Dr. Whitlon aims to identify the most effective oral statin to protect against noise-induced hearing loss and cochlear damage and to investigate its effect, either alone or in combination with oral steroids, in both a noise-induced hearing loss animal model and in a pilot, first-in-kind clinical trial with human idiopathic sudden sensorineural hearing loss patients. If successful, this work has the potential to significantly lower the incidence of noise-induced hearing loss among military personnel and civilians alike.

"Almost every man and woman who served our country suffers from some hearing loss or other hearing-related challenge. It's an ongoing battle that we face for the rest of our lives. As a disabled Veteran who suffers from hearing loss and vertigo, I cannot overstate the importance of the HRRP. This program holds the potential to mitigate the impact of this widespread health issue and thereby greatly improve the quality of life for our nation's Veterans. It's an honor and a privilege to continue to serve our nation as a part of the effort to significantly improve the lives of our Service members and Veterans."

Todd S. Desgrosseilliers, Colonel, US Marine Corps (Retired), Project Healing Waters Fly Fishing, Inc., HRRP Programmatic Panel Consumer Representative

JOINT WARFIGHTER MEDICAL RESEARCH PROGRAM

Program History

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

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

Congress first appropriated $50M for the JWMRP in FY12 and again in FY13; later doubling the appropriation to $100M in FY14, followed by $50M per fiscal year in FY15-FY19 and $40M in FY20. Because the overall goal of the program is to deliver a product for the DOD, the proportion of funding available for advanced technology development initiatives has been adapted over the years. A total of 28 projects were funded by the JWMRP in FY12, 35 in FY13, 46 in FY14, 30 in FY15, 34 in FY16, 27 in FY17, 17 in FY18 and 13 in FY19. The graph below depicts the program investments for FY19.

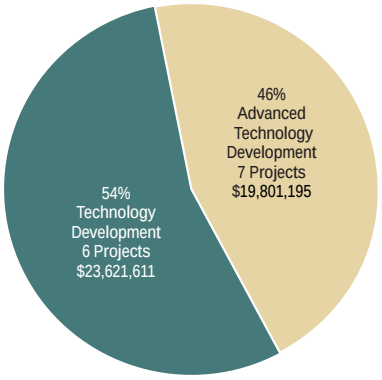
The JWMRP is a dynamic program that facilitates maturation of previous congressionally and core programmed funded efforts that demonstrate the potential to close identified military medical capability gaps. By focusing on both early and advanced technology development, the JWMRP provides a pathway to transition products to military healthcare providers and the warfighter.

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**

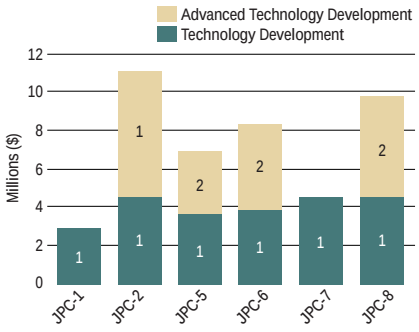
Mission: **Accelerate research and development projects that have the potential to close high priority Department of Defense medical capability gaps**

"JWMRP has been vital in supporting the Navy to accelerate a multiple prototype strategy for bacteriophage. Armata Pharmaceuticals - the selected award recipient - will continue to validate the potential for phage-based therapeutics with a second clinical program testing a targeted phage cocktail to treat Staphylococcus aureus bacteremia."

Mr. Thomas Dunn, Navy Advanced Development Representative, Navy Medical Research Center



FY19 JWMRP Investment (% of total FY19 Investment)



FY19 JWMRP Final Funding Distribution (Number of Awards Granted Indicated in Each Bar Chart)

Research and Product Development Efforts Funded by the JWMRP Include:

Technology Readiness Level

4

- Focused effort on improving cognitive and functional deficits in individuals with TBI using virtual technology
- Development of a thermoresponsive reversible adhesive for temporary intervention of ocular trauma
- Accelerating development of freeze dried plasma in a combat ready rugged lightweight container
- Treatment of adult severe TBI using autologous bone marrow mononuclear cells

- Development of an implantable pudendal nerve stimulator to restore bladder function in humans after spinal cord injury
- Phase III clinical trial of Peripheral Nerve Stimulation System for improving functional outcomes by alleviating pain in individuals with major lower limb amputations

- IND-enablement of Kinocidin Gamma-RP-1 for multidrug-resistant gram-negative infections
- Development of a novel product for temporary corneal repair
- Development of BIO301 as an oral prophylactic and post-exposure treatment for acute radiation syndrome

5

- Development of a lyophilized injectable for a point-of-care therapeutic for post-traumatic osteoarthritis
- Phase I clinical trial for a direct acting polymyxin antibiotic to treat multidrug resistant gram-negative pathogens
- Phase II/III clinical tiral of Riluzole for spinal cord injury
- Phase I/II clinical trial of Bacteriophage for Treatment of Bacterial Infections

6

- Development of a moisture management liner and active cooling system for lower limb prostheses to improve fit, comfort, and residual limb skin care

7

- Device development of the Transportable Pathogen Reduction and Blood Safety System
- Development of a non-electric, disposable intravenous infusion pump

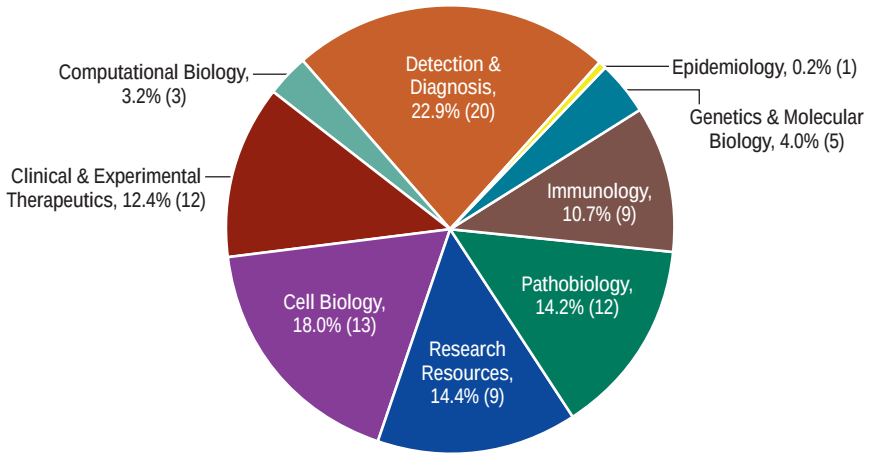
KIDNEY CANCER RESEARCH PROGRAM

Kidney Cancer impacts US Service members, their dependents, and Veterans

Occupational exposures unique to active Service, such as ionizing radiation or chemical and/or hazardous materials can cause kidney cancer, though the disease may not appear until later in life.[1] These exposures have resulted in Veterans being more frequently affected than their US civilian counterparts. According to a 2014 report by the Centers for Disease Control and Prevention, US Marines and their families stationed at Camp Lejeune, North Carolina, have a 35% higher risk of contracting kidney cancer than civilians, due to contaminated drinking water.

Program History

The Peer Reviewed Kidney Cancer Research Program (KCRP) was established by Congress in FY17 with $10M to address critical research needs facing the kidney cancer community. During the inaugural year of the program, KCRP held a Stakeholders meeting to gain an understanding of the current landscape in kidney cancer research and patient care and to build a program that would fill outcomes and knowledge gaps in kidney cancer. As a result of the continued efforts of kidney cancer advocates, KCRP received congressional appropriations of $15M for FY18, $20M for FY19, and $40M directed to the program for FY20. In all, between FY17 and FY20, Congress has directed $85M to support kidney cancer research. The KCRP has funded 84 awards to support high-impact research in prevention, detection, treatment, and to bring talented investigators into the field. For FY19, KCRP offered funding mechanisms designed to foster innovative research, provide opportunities for early-career investigators, mentor and prepare young investigators for productive kidney cancer research careers within a virtual Academy, support collaborations between clinicians and scientists, and establish a preeminent clinical trials consortium to speed development of promising new therapies.



KCRP FY17-FY19 Portfolio Investment by SCS Code (Number of Awards)

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**

"In 2007 when my husband Gary was diagnosed with widely metastatic kidney cancer there were few treatment choices... I quickly learned that my career in radiation oncology as a medical physicist gave me a unique perspective for both patient and research support, and I felt a call to help. In 2019 I joined the KCRP as a consumer advocate reviewer. It was an amazing experience to sit with other advocates, physicians, and researchers and discuss each proposal. Every voice was heard and I left feeling that those ideas ...were the foundations for the next generation of progress toward understanding kidney cancer."
Susan Poteat, KidneyCAN.org, KCRP Programmatic Panel Consumer Advocate Reviewer

[1] National Research Council (US) Committee on Contaminated Drinking Water at Camp Lejeune. 2009 Contaminated Water Supplies at Camp Lejeune: Assessing Potential Health Effects. Washington (DC): *National Academies Press* (US)

Research Highlights

Traditional cancer treatments, including chemotherapy, radiation, and surgery, all focus on directly attacking cancer cells. In contrast, a newer category of cancer treatments, called immunotherapies, encourage and improve the patient's own immune system to recognize and attack cancer cells. Chimeric Antigen Receptor (CAR)-T cell therapy is a type of individualized and personalized immunotherapy. T cells are extracted from the patient and then exposed to engineered viruses that program the T cells to express specific CARs, which directly target cancer cells; the CAR-T cells are then proliferated in culture and re-introduced into the patient. While CAR-T cell therapies have demonstrated clinical utility for hematologic cancers, such as leukemia and lymphoma, so far there has been limited translation of these therapies to targeting and treating solid tumors. Thus, current efforts are focused on the use of CAR-T cell therapy to target more cancer types, including kidney cancer. Renal cell carcinoma (RCC) is the most common kidney cancer, it initiates in the cells that form the lining of kidney tubules. Clear cell carcinoma (ccRCC), papillary cell carcinoma, and chromophobe carcinoma are the three main types of RCC. The KCRP supports several innovative immunotherapy-related research efforts directed at kidney cancer, including the two projects highlighted below.

Targeting B7-H3 in Metastatic Renal Cell Carcinoma Using CAR-T Cells

Hongwei Du, Ph.D., University of North Carolina at Chapel Hill

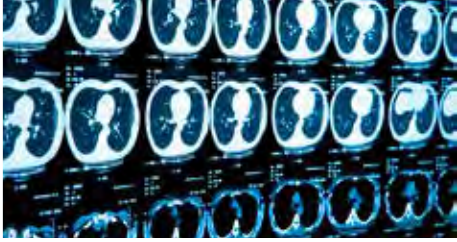
Dr. Du and his team previously discovered that B7-H3, an immune checkpoint membrane protein, is highly expressed on tumor cells and conservatively expressed on normal tissues. Further studies led to the development and pre-clinical evaluation of B7-H3 targeted CAR-T cells (B7-H3.CAR-Ts). These CAR-T cells have implications for treatment of several cancers. Dr. Du's initial discoveries resulted in a patent application (20180371053A1), a publication in *Cancer Cell*,[2] and Phase I clinical trials in ovarian cancer. With support from a KCRP FY17 Concept Award his team expanded the B7-H3.CAR-Ts studies to kidney cancer. Initial flow cytometry results confirmed B7-H3 was B7-H3 was positively expressed in cell lines of all three main types of RCC and not in normal kidney tissue. Then, CAR-T cells targeting B7-H3 positive RCC cells were generated and cultured with RCC cells. Results confirmed antitumor activity, noting restricted tumor cell growth as well as increased cytokine release compared to RCC cells treated with negative control CD19. CAR-Ts. The team then injected the metastatic RCC mouse model and orthotopic RCC mouse model with B7-H3.CAR-Ts and similarly confirmed antitumor activity; mice treated with B7-H3.CAR-Ts were tumor-free more than 60 days post-treatment, while mice treated with CD19.CAR-Ts developed sizeable tumors. The next step planned for this research includes an evaluation of B7-H3.CAR-Ts' ability to access tumor and reduce tumor growth in mouse models expressing B7-H3 positive vasculature. If successful, Dr. Du's work could potentially lead to evaluating B7-H3.CAR-Ts for kidney cancer treatment in clinical trials.

[2] Du H, Hirabayashi K, Ahn S, et al. 2019. Antitumor responses in the absence of toxicity in solid tumors by targeting B7-H3 via chimeric antigen receptor T cells. *Cancer Cell* 35(2):221-237.e8. doi: 10.1016/j.ccell.2019.01.002.

Use of Anti-CAIX/CD70 Bispecific CAR-T Cell Factories to Achieve RCC Cures

Wayne Marasco, M.D., Ph.D., Dana-Farber Cancer Institute

With the support of a FY17 Idea Development Award – Established Investigator, Dr. Marasco and his team aim to translate CAR-T cell therapy into ccRCC treatment by restoring the active anti-tumor tumor microenvironment. They designed immune restoring CARs (IR-CARs) which enables CAR-T cell to secrete checkpoint blockade inhibitors at the tumor site to prevent CAR-T exhaustion and reverse tumor infiltrating lymphocyte exhaustion. The team elevated both efficacy and safety profiling of IR-CAR T cells by introducing the dual antigen recognition technology (DART) and fine-tuning engineering. DART enables CARs to recognize two different antigens that are expressed on the majority of solid tumor cells. By fine-tuning the avidity of CAR, Dr. Marasco's team found that the two targeting moieties selectively bind only to the overexpressed antigens on tumor cells and not to the low expressed antigens on healthy cells. Currently, Dr. Marasco's team validated DART for targeting Carbonic Anhydrase IX (CAIX) and CD70 that are overexpressed on the majority of ccRCC and has been validated by immunohistochemistry staining on patient tumors. Panning against a 27 billion-member human single chain variable region fragment (scFvs) phage display library, a series of anti-CD70 scFvs were identified, in which B7 was evaluated as a candidate and assembled to the DART construct. At present, B7-linker3-G36 secreting anti-PD-L1 monoclonal antibody is considered as the lead IR-CAR. Dr. Marasco has submitted provisional patent applications for the new IR-CARs. He hopes to move this promising therapy quickly into clinical trials upon demonstration of safety and efficacy in animal studies.



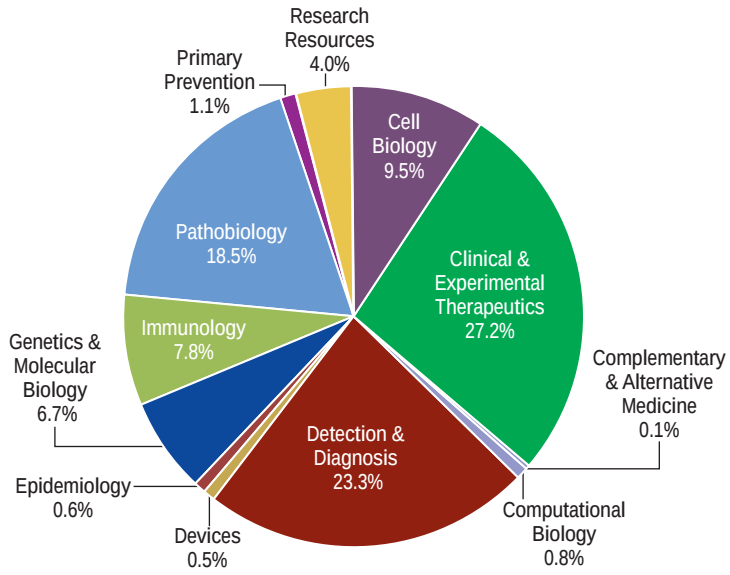
LUNG CANCER RESEARCH PROGRAM

Program History

The DOD Peer Reviewed Lung Cancer Research Program (LCRP) was established in FY09 with a congressional appropriation of $20M, and since that time it has received a total of $155.5M in congressional appropriations through FY20. During the past 11 years, 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. To address the critical needs of the lung cancer research and patient community, the LCRP adapts its investment strategy annually, focusing its support on underfunded and underrepresented areas.

Lung Cancer Impacts US Service Members and Veterans

Lung cancer is the leading cause of cancer mortality, accounting for 22% of all deaths.[1] Lung cancer risk for our military is significant, with 24% to as high as 38% of Service members smoking, compared to 14% of civilians.[2] Deployments also worsen smoking rates by about 50%. Among military Veterans, 29% reported current tobacco use.[3] According to a 2010 update on cancer incidence among patients of the US Veterans Affairs Health Care System, over 8,200 Veterans per year are diagnosed with lung cancer[4] and an estimated 900,000 Veterans remain at risk due to age, smoking, and other environmental exposures during and after military Service.



FY09-FY19 LCRP Portfolio Investment by SCS Code

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

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

"I am now in my third year as a consumer reviewer, and it has been every bit as rewarding as I had hoped it would be.... I feel tremendous hope for the future when I get to see what the researchers are working on, and I am always honored and humbled to share a conference table with the brilliant scientists who are superheroes to me and my fellow patients. To be able to provide the patient perspective on proposed research is a gift that I cherish, and I take great pride in the work I have been able to do for the LCRP."
Sarah Christ, LCRP Consumer Peer Reviewer

[1] https://seer.cancer.gov/statfacts/html/common.html

[2] US Secretary of Defense. 2016. Memorandum for Secretaries of the Military Departments. Washington, DC: US Secretary of Defense.

[3] Odani S, Agaku IT, Graffunder CM, et al. 2018. Tobbaco product use among military veterans - United States, 2010-2015. *MMWR Morb Mortal Wkly Rep*. 67:7-12.

[4] Zullig LL, Sims KJ, McNeil R, et al. 2017. Cancer incidence among patients of the US Veterans Affairs Health Care System: 2010 Update. *Mil Med* 182(7):7/8:e1883.

Research Outcomes

Discovery & Preclinical	Phase I	Phase II	Phase III
Multiple LCRP preclinical projects have shown great success, their results providing the basis for advancing to clinical trial testing.	• NCT02520778: Osimertinib and Navitoclax in Treating Patients with EGFR-Positive Previously Treated Advanced or Metastatic Non-Small Cell Lung Cancer (NSCLC) (Phase 1) • NCT02071862: Study of the Glutaminase Inhibitor CB-839 in Solid Tumors (Phase 1)	• NCT04263090: Rigosertib Plus Nivolumab for KRAS+ NSCLC Patients Who Progressed on First-Line Treatment (Phase 1/2) • NCT02414269: Malignant Pleural Disease Treated with Autologous T Cells Genetically Engineered to Target the Cancer-Cell Surface Antigen Mesothelin (Phase 1/2)	• NCT04214262: Testing the Addition of the Drug Atezolizumab to the Usual Radiation Treatment for Patients with Early Non-Small Cell Lung Cancer (Phase 3)

Funding support for the listed clinical trials is currently provided by funding organizations other than LCRP.

In the Pipeline: Moving Promising Ideas into Clinical Applications

A Novel Agent for Lung Cancer Prevention

Arun Sharma, Ph.D., The Pennsylvania State University

Dr. Sharma received an Investigator-Initiated Translational Research Award to evaluate the potential of p-XS-Asp (conjugated from two chemopreventive agents: 1,4-phenylenebis(methylene)-selenocyanate and aspirin) to be a lung cancer preventive agent capable of inhibiting lung tumorigenesis at initiation and post-initiation stages. Dr. Sharma's team aims to study p-XS-Asp as a dietary supplement in animal models, elucidating stage-specific effects and the mechanism of action for translatability into humans. If successful, p-XS-Asp will give hope of preventing lung cancer to high-risk individuals, such as those exposed to abnormally high levels of carcinogens.

Novel Imaging Agent for Metastatic NSCLC Diagnosis and Prognosis

Megan Daly, M.D., and Julie Sutcliffe, Ph.D., University of California, Davis

The cell surface receptor alphaVbeta6 integrin is overexpressed in NSCLC and several other cancers, but remains undetectable in healthy epithelium. With support from a Translational Research Partnership Award Drs. Daly and Sutcliffe are developing a PET /CT -traceable peptide targeting alphaVbeta6 integrin to distinguish cancerous tissue from healthy tissue in metastatic NSCLC patients. They anticipate this technology will improve specificity of imaging diagnostics and prognostics for lung cancer, and help identify patients that would benefit from treatment that targets alphaVbeta6 integrin, including NSCLC patients with brain metastases.

Targeting Mitochondria Bioenergetics in Immune-Cold NSCLC

David Shackelford, Ph.D., University of California, Los Angeles

NSCLC patients are often resistant to immunotherapy, in which the fast-growing tumors are "immune-cold." These tumors rely heavily on mitochondrial oxidative metabolism to grow. Dr. Shackelford's lab received an Investigator-Initiated Translational Research Award to develop a novel PET agent capable of non-invasive, in vivo visualization of mitochondrial oxidative phosphorylation (OXPHOS) activity to help identify and target metabolically aggressive tumors. Eventually, the team hopes to develop a new therapeutic strategy of starving aggressive tumors to limit growth via inhibiting mitochondrial OXPHOS and glycolysis activity.

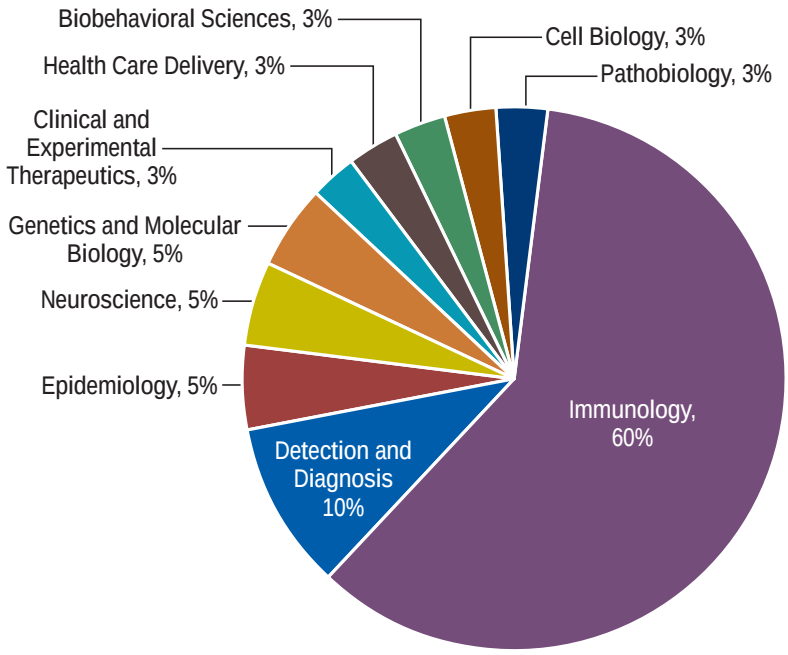
LUPUS RESEARCH PROGRAM

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

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

Program History

Lupus is a chronic, heterogeneous autoimmune disease that is difficult to diagnose and treat. Approximately 90% of lupus patients are women, and the disease is more common in women of African American, Hispanic, Asian, and Native American descent than in Caucasian women. Lupus can cause inflammation in the skin, joints, kidneys, lungs, heart, and brain. Because it affects numerous parts of the body, people living with lupus experience a wide range of symptoms including fatigue, arthritis, headaches, weight loss, organ damage, seizures, and strokes. The severity of symptoms can be exacerbated if a patient is experiencing a lupus flare. Treatment options for lupus are highly dependent on an individual patient's symptoms and can include nonsteroidal anti-inflammatory drugs and corticosteroids. Patients are frequently treated with a combination of drugs. Because the symptoms of lupus vary from person to person, the disease is difficult to diagnose. There is currently no single test available capable of diagnosing lupus. CDMRP has funded lupus research as a topic area within the Peer Reviewed Medical Research Program (PRMRP) from FY05-FY16. During this time, the PRMRP funded 21 lupus research awards for a total of $20.6M. In FY17 the Peer Reviewed Lupus Research Program (LRP) was established with an appropriation of $5M. Since then, a total of $20M has been appropriated to the program, including an increase in appropriations to $10M in FY20. The LRP has funded 38 awards through FY19 to support innovative, high-risk, high-reward studies that offer the promise of shifting current paradigms with the hope of improving treatments and quality of life for those living with lupus.



LRP FY17-FY19 Portfolio Investment by SCS Code

LRP Research Outcomes

Systemic Lupus: Improving the Rationale for Treatment Choices in a Heterogeneous Disease

Joan Merrill, M.D., Oklahoma Medical Research Foundation

In FY17, Dr. Joan Merrill was awarded a LRP Impact Award to determine whether lupus patients with a particular immune signature are more likely to respond to methotrexate, a commonly used lupus treatment. Dr. Merrill's team is utilizing data collected from previously completed clinical trials to create a database and tease out differences in how various combinations of individual and overlapping treatments impact the immune phenotypes and gene expression levels in patients. With the support from the LRP, Dr. Merrill's team was able to retrospectively collect, match, and validate 564 paxgene samples, 543 plasma samples, and complete clinical data (including medication history and disease state) from 154 individual patients from previously completed clinical trials to provide samples from active/inactive disease on no immune suppressants, methotrexate, and other common treatments to use as controls. The team was able to evaluate the expression of immune-modulated genes and group patients into similar subpopulations, or clusters, based on their phenotypes expressed. Through this extensive effort, Dr. Merrill was able to reproduce and statistically confirm the preliminary findings to phenotypically group a range of patients with high and low disease activity while taking methotrexate versus control medications, into seven unique clusters. Dr. Merrill has completed the first step of many to collect and develop a large and complete dataset for study. In fact, as the Clinical Trial Project Leader, she is currently leveraging results from this work in a clinical trial recently funded by the National Institute of Allergy and Infectious Diseases – Oklahoma Autoimmunity Center of Excellence: Molecular Deconstruction of Autoimmune Disease to Aid Clinical Trial Success (1UM1AI144292; Principal Investigator is Dr. Judith James).

Utility of a Functioning Report for Lupus Patients and Their Providers

Laura Plantinga, Ph.D., Emory University

In 2017, Dr. Laura Plantinga was awarded a LRP Concept Award to improve recognition of and facilitate discussion around the issue of functional impairment in systemic lupus erythematosus (SLE) patients. Dr. Plantinga aimed to determine how useful a physical functioning report could be to capture, visualize, and quantify functional impairment in an understandable manner for patients and healthcare providers. Dr. Plantinga's team modified an app that was originally developed to create functioning reports for end-stage renal disease so that it was compatible with SLE data. Data from a recent pilot study, in which 60 SLE patients underwent assessments of physical and cognitive functioning, were leveraged to create the app-generated reports. Each report gave the results from self-reports and physician guided exams, including sections rating a patient's ease of performing everyday activities, their concern for falling, and their mobility. Of the patients involved in the leveraged study, 59 of 60 received reports generated by the app, and researchers administered a survey to determine how easy the results were to interpret and how likely patients and healthcare providers were to discuss the results. Ease of interpretation ranged from 70.2% to 85.1%, and 70.2% to 80.5% felt that the report was useful for treatment. Almost all patients (93.2% to 100%) responded that they would be comfortable discussing the results with a healthcare provider. Interest in receiving a real-time report was reported by 87.2% of patients, and 89.1% expressed a willingness to arrive early to an appointment to receive one. Dr. Plantinga's team continues to complete quantitative analysis of the survey results. They plan to build an app to produce reports for cognitive functioning similar to those created for physical functioning in this study.

"Serving on the LRP allowed me to continue doing what I have done my entire Army career, to serve my country. Through the LRP I was able to serve my lupus community and to have a voice as a lupus patient with regards to future innovative treatments, therapies, and research. It has been a true honor."
MAJ Toni Grimes, Retired, US Army, Lupus Foundation of America, LRP Consumer Peer Reviewer

MELANOMA RESEARCH PROGRAM

Program History

Melanoma is one of the most aggressive types of skin cancer. According to the National Cancer Institute, it's estimated that there will be 100,350 new cases of melanoma diagnosed in the US during 2020. It is the fifth most common type of cancer in the US, representing 5.6% of all new cancer diagnoses. Research suggests that exposure to high levels of solar radiation in young adulthood is associated with a higher risk of melanoma mortality. According to the 2018 Military Demographics (https://download.militaryonesource.mil/12038/MOS/Reports/2018-demographics-report.pdf), 52.3% of active duty enlisted personnel are under the age of 25 years with another 20.7% between the ages of 26-30 years old. Another 22.4% are between the ages of 31-40 years. Melanoma diagnoses are increasing among active duty Service, with the greatest incidence rates in the Air Force, Navy, and the Marines. Given deployments around the world, especially in areas of high ultraviolet radiation (UV), Service members are exposed to initiators of melanoma. Due to the rise of this aggressive and frequently deadly form of cancer, the US Congress established the Peer Reviewed Melanoma Research Program (MRP) in the DOD. From FY19 through FY20, Congress has appropriated $30M for the MRP, which has been invested in research focusing on the prevention, detection, diagnosis, and treatment of melanoma for the benefit of Service members, Veterans, their families, and the American public.

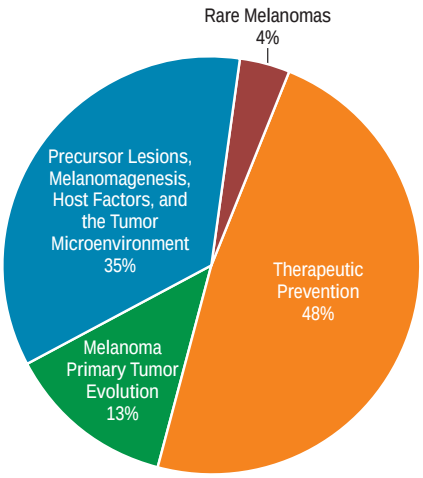
Vision: **Prevent melanoma initiation and progression**

Mission: **Earlier intervention to enhance mission readiness for US military personnel and to diminish the disease burden on Service members, Veterans, and the American public**

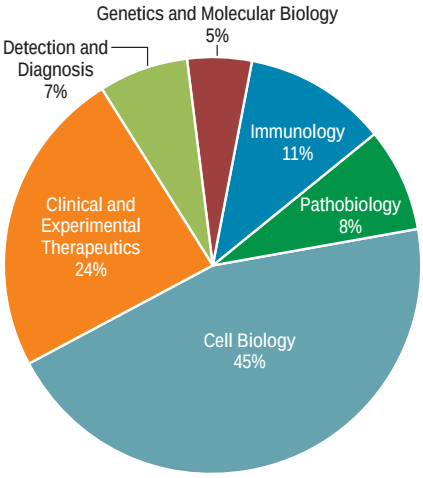
FY20 Focus Areas

- Prevention of melanoma initiation factors (e.g., UV radiation)
- Prevention of melanomagenesis and precursor lesions (e.g., novel genetic and epigenetic drivers, oncogene induced senescence)
- Understanding the tumor microenvironment
  - Primary Tumor
  - Regional Nodes
  - Distal Nodes
- Bioengineering (e.g., computational, imaging) approaches to address diagnostics, high risk markers, dormancy, and metastasis
- Therapeutic Prevention (e.g., interruption of disease progression, recurrence)
- Minimal Residual Disease (e.g., chemoprevention, micro-metastasis)

"The unique spirit of collaboration between public and private sector scientists and laypeople on the MRP programmatic panel created a strong alliance of synergistic knowledge, resulting in a very impactful outcome. It was a privilege to be a part of this collective effort."
Ellen Davis,
MRP Consumer Reviewer



FY19 MRP Portfolio Investment by Focus Area



FY19 MRP Portfolio Investment by SCS Code

References:
Lea CS, Efird JT, Toland AE, et al. 2014. Melanoma incidence rates in active duty military personnel compared with a population-based registry in the United States, 2000-2007. *Military Medicine* 179(3):247-253.

Riemenschneider MD, Liu J, and Powers JG. 2018. Skin cancer in the military: A systematic review of melanoma and nonmelanoma skin cancer incidence,prevention, and screening among active duty and veteran personnel. *JAAD* 78(6):1185-1192.

In its inaugural year, the FY19 MRP funded 19 awards, representing 16 unique projects, through 4 award mechanisms: Idea Award, Team Science Award, Translational Research Award, and Concept Award. The projects below represent some of the promising research supported by the MRP.

FY19 Idea Award

Targeting Acral Melanoma by Inducing TERT Degradation
Jessie Villanueva, Ph.D., Wistar Institute
Acral lentiginous melanoma (ALM) is a subtype of melanoma that develops on the palms, soles, or nail beds. Genomic alterations in the telomerase reverse transcriptase gene (TERT) are present in over 40% of ALM cases. TERT is silenced in most normal cells, making it an attractive therapeutic target; thus drugs targeting TERT are expected to specifically affect cancer cells. By focusing on abolishing TERT function, Dr. Villanueva hopes to inhibit the progression of ALM.

The Kinome of GNAQ/11-Mutant Uveal Melanoma
Andrew Aplin, Ph.D., Thomas Jefferson University
Currently, there are no FDA-approved therapies for metastatic uveal melanoma, the most common ocular malignancy in adults. Dr. Aplin's team aims to understand the signaling pathways downstream of GNAQ and GNA11 mutations, genes known to be mutated in uveal melanoma. Understanding these signaling mechanisms could lead to the development of targeted therapeutics.

FY19 Team Science Award

Improving the Diagnosis of Melanoma and Precursor Lesions Among Veterans: Developing Artificial Intelligence (AI) Techniques and Teledermatopathology
Joann Elmore, M.D., University of California Los Angeles (shown left)
Linda Shapiro, Ph.D., University of Washington (shown right)
Drs. Elmore and Shapiro's project aims to develop a VA-wide teledermatopathology system to improve the clinical care of the VA population with melanoma and its precursors. To achieve this, the team will assess pathologists' viewing behaviors to support their goal of developing an AI tool that may be used to support pathologists' interpretations in order to improve diagnostic accuracy.

FY19 Translational Research Award

Immune Profiling of Sentinel Lymph Nodes in Melanoma
Mark Faries, M.D., Cedars-Sinai Medical Center
Dr. Faries' team will examine the immune microenvironment in sentinel lymph nodes over the course of a melanoma patient's disease progression and response to treatment. Disease recurrence and response to checkpoint inhibitor therapy will be analyzed in order to understand how melanoma evades the immune response during the metastatic process.

FY19 Concept Award

Targeting the Oncoprotein RLIP as Novel Therapy for Melanoma
Sharad Singhal, Ph.D., City of Hope Beckman Research Institute
Oxidative stress enzymes are overexpressed in melanocytes during melanomagenesis. Dr. Singhal's research will focus on RLIP, a cell membrane transporter protein important for oxidative stress signaling, and whether it can be targeted to inhibit UV-induced melanomagenesis.

MILITARY BURN RESEARCH PROGRAM

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

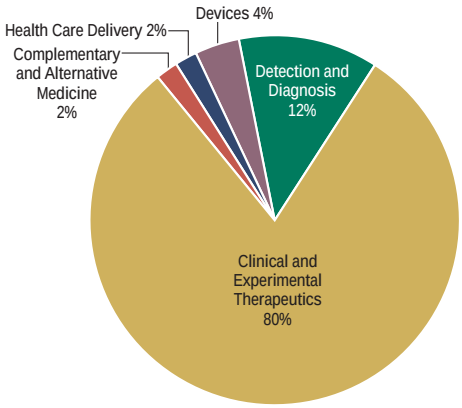
Mission: Identify and address gaps in burn trauma care through military focused translational research

"Out of all the different programs that exist, both in the CDMRP as well as the NIH and other intra-agency funding programs, the Military Burn Research Program is the only program dedicated to burns. And that's—that's what makes it unique."
COL Kevin Chung, MBRP Programmatic Panel Chair

Program History

According to the American Burn Association, nearly 500,000 patients in the United States require treatment for burn injuries annually, with 40,000 of those patients requiring acute inpatient care, and an average of 3,000 patients die annually from burn injuries.[1-2] Military burns are often devastating and more severe than burns obtained in the civilian setting. The majority of combat burns result from explosive device detonation, leading to a greater Injury Severity Score, an increase in inhalation injuries, and a larger, full-thickness burn size. Burns have comprised some 5%-20% of the casualties sustained in post-World War II conflicts.[3]

The Peer Reviewed 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 more than $70M has been appropriated to the program by Congress. Through FY19, MBRP has funded 49 research projects that have provided key research insights in advancing therapies for burn-injured patients and impacting standard practice.



FY11-FY19 MBRP Portfolio Investment by SCS Code

Strategic Priorities

The military burn field has benefitted from many successes; however, many challenges and gaps still exist that drive the research funded by the Program. The MBRP has established four priorities around which it will continue to build its funding efforts:

- Development of interventions or therapies that can help, accelerate, or optimize wound healing.
- Development or refinement of interventions or technologies that will enable non-burn specialists, such as a field medic/corpsman/paramedic, to provide good burn care closer to the point of injury, allowing for better long-term outcomes.
- Development of therapeutic interventions that can help treat debilitating scars and prevent contractures.
- Advancement of standard of care practices through conduct of high impact clinical trials.

Future priorities of the MBRP include research topics that are contingent on the success of research and interventions being developed by others in and outside of the burn field. The MBRP will continue to monitor outcomes of these related fields in order to determine the Program's role in assessing the epidemiology of burn injuries to better identify the gaps in knowledge and care for burn patients, driving clinically focused research to assess the safety and efficacy of existing burn treatments, and supporting high impact clinical trials to advance the standard of burn care.

[1] Delaplain P and Joe V. 2018. Problems and costs that could be addressed by improved burn and wound care training in health professions education. *AMA J Ethics*, 20(6):560-566.

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

[3] 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.

Recent MBRP Research Outcomes

A Phase 1 Randomized, Placebo-Controlled, Single Ascending Dose Study to Examine the Safety, Tolerability, and Pharmacokinetics of cP12 in Healthy Adults

Richard Clark, M.D., NeoMatrix Therapeutics, Inc.

NeoMatrix Therapeutics, Inc. (NMT), a clinical stage company, is developing a drug candidate, cP12, that accelerates burn wound healing by moderating the progression of tissue damage in areas surrounding a burn. cP12 has received both orphan drug and Fast Track designation from the FDA. Under an IND Application, NMT has completed a placebo-controlled Phase I trial that assessed the safety and tolerability of single ascending intravenous doses of cP12 in healthy subjects and measured its pharmacokinetic profile following dose administration. The drug was shown to be safe in the 24 participants in four cohorts, each of which received an ascending dose of cP12. Subsequent to the completion of dosing as described in the initial Phase I protocol, NMT received approval from the FDA to add an additional cohort of six participants to extend those who received a dose of cP12 that was higher than that mandated by the original protocol. Based on successful completion of the Phase I trial, NeoMatrix is now planning a multi-center, Phase IIa clinical trial to assess the safety of cP12 in patients with 5% to 20% total body surface area burns, as well as its efficacy in mitigating burn injury progression measured by a primary outcome of enhanced wound closure at 21 days post-burn.

A Goniometry Paradigm Shift to Measure Burn Scar Contracture in Burn Patients

Ingrid Parry, MS, PT, BT-C, United States Army Institute of Surgical Research

Ms. Ingrid Parry and her research team led a multi-center clinical research study to examine the validity of the current goniometry (the measurement of range of motion in a joint) method for determining functional outcomes for burn patients with scar contractures. They compared standard goniometry to a newly developed revised paradigm based on cutaneokinematic factors, which considers skin recruitment for range of motion. The revised goniometry, taking into account the positions impacted by the scar contractures, determined significantly more limitation in joint motion than assessments made by the standard goniometry. The study team received several awards and have published their study results in March 2019 in the *Journal of Burn Care and Research*. Ms. Parry also led the development of an application, called "Scar Goniometry," available for download onto Apple and Android smart devices, to guide other physical therapists interested in using the revised goniometry methods for improving the assessments of functional outcomes for patients with burn scars.

Omega-3 Fish Skin for Burn Wound Coverage and Advanced Healing

Hilmar Kjartansson, M.D., Kerecis Limited

Kerecis Limited has obtained FDA approval for its fish skin technology, Omega3 Wound, to treat chronic wounds, and 501(k) cleared fish skin products to treat trauma wounds, including second-degree burns. With a FY15 Burn Injuries Research Award, Kerecis Limited and Dr. Kjartansson advanced their Kerecis® fish skin technology as a potential alternative to human cadaver skin (current standard of care) to provide temporary burn wound coverage in the treatment of deep-thickness and full-thickness burns. The safety and efficacy of the Kerecis fish skin graft were demonstrated to provide temporary burn wound coverage in a relevant pig model with full-thickness burns (third-degree burns) following debridement. In another porcine animal model with deep-partial burns (deep second-degree burns), the fish skin product again provided better wound healing than fetal bovine dermis, a substitute for allograft to treat large burn injuries, producing a granulated wound bed much faster, by Day 14 compared to Day 21, and demonstrated faster re-epithelialization, improved wound healing with or without autografts, and improved contraction. The fish skin alternative is currently being tested in a small pilot clinical study to assess its safety, efficacy, and establish the clinical relevance of the Kerecis-modified fish skin product for third-degree burns in humans.

"Burns are one of the most devastating injuries. Disfigurement, chronic pain, and the constant medical procedures can lead to depression, then suicidal ideation which Service members/Veterans are more likely to act on. Knowing that we can not only save lives, but also provide a better quality of life after injury is why I will continue to serve the burn community."

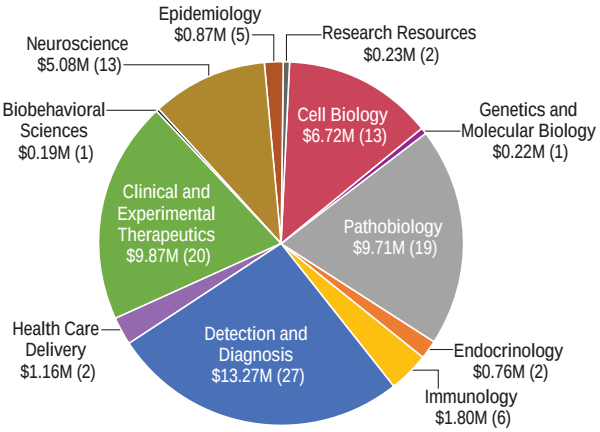
SSG James West, MBRP Programmatic Panel Member, Consumer

MULTIPLE SCLEROSIS RESEARCH PROGRAM

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 $73.1M 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 over 111 projects, including 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.

In FY20, the Congress increased the MSRP appropriation from $6M to $16M. This has enabled the MSRP to expand its mission to include the understanding of the various risk factors of the disease etiology and disease course, and clinical trials to evaluate innovative interventions that promote repair, neuroprotection, and remyelination, as well as approaches that can have a profound impact on the management of MS symptoms.



FY09-FY19 MSRP Portfolio Investment by SCS Code (Numbers of Awards)

Military Relevance

MS has a higher incidence in US Armed Forces personnel than in the general population. Between 2009 and 2018, more than 2,400 active duty and reserve and National Guard Service members received a new diagnosis of MS within the Military Health System. Including other DOD beneficiaries such as former Service members and family members, the Military Health System had more than 21,000 new cases of MS. During this period, more than 36,000 DOD beneficiaries had over 1.1 million outpatient encounters and 537,000 hospital bed days for MS within the Military Health System. In addition, the Department of Veterans Affairs Multiple Sclerosis Centers of Excellence, East and West branches, serve approximately 30,000 Veterans with MS.

Program Goals

1. Understand, measure, and treat relapsing and progressive aspects of MS
2. Identify strategies for neuroprotection, repair, and restoration of function, and ultimately improving symptoms and quality of life
3. Elucidate the cause and pathophysiology of MS symptoms that have a high impact on quality of life and develop treatment strategies
4. Identify the role of various risk factors (genetics, environment, race and ancestry, age, comorbidities, risk behaviors, etc.) in MS etiology and disease course

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**

"I proudly watched the MSRP develop into a vital program that solidly put multiple sclerosis on the research map. It is now my privilege to serve as a MSRP consumer reviewer! I look forward to sharing my MS story with the scientists and clinicians who seek to move us further along the road to living our best lives with MS. We've come a long way from no treatments to injectables to so many treatment options today. Let's keep moving forward!"
Nancita Rogers, National Multiple Sclerosis Society, MSRP Programmatic Panel Member

Research Accomplishments

Online Toolkit to Assist with Self-Management of MS Symptoms

Anna Kratz, Ph.D., University of Michigan

With a FY16 Exploration – Hypothesis Development Award, Dr. Kratz and her collaborators, Dr. David Williams from the University of Michigan and Drs. Dawn Ehde and Kevin Alschuler from the University of Washington, developed and tested a WEB-SM program to manage fatigue, pain, and depressed mood in persons with MS. The goals of this program, called My MS Toolkit (www.mymstoolkit.com/), are to provide evidence-based education, guidance, and skills-building exercises that are specifically tailored for people with MS. Through all stages of development, the investigators worked with a stakeholder panel of individuals with MS who provided ongoing feedback on the content and format of the website to ensure the usability/accessibility and relevance of My MS Toolkit to those with MS. They then performed pilot testing in a group of 20 people with MS who reported clinically significant pain, fatigue, and/or depressive symptoms. Pilot study participants completed pre-treatment outcome measures, followed by 12 weeks of intervention (self-guided use of My MS Toolkit), and then a battery of post-treatment outcome measures. Through this pilot work, the researchers are evaluating the impact of My MS Toolkit on the user's self-efficacy to manage symptoms, global perceptions of change, and treatment response in terms of symptom reduction pre- to post-intervention. The study is in the final phase of data analysis, and outcomes related to initial effects of the treatment are expected to be published this year. My MS Toolkit is freely available to the public. Dr. Kratz's work will provide a supportive tool for clinical care teams and individuals as a complement to their medical support team.

Tap Your Feet to Track Progressive MS

Richard Van Emmerik, Ph.D., University of Massachusetts Amherst

With support from a FY15 Investigator-Initiated Research Award, Dr. Van Emmerik and his team have been studying coordination and control of human movement and how different sensorimotor measurements can identify patients who have progressive MS (PMS). Specifically, the investigators studied rapid hand or foot tapping ability measured by inertial sensors worn on the hand or foot in relapsing remitting MS (RRMS) and PMS compared to non-MS controls. They observed that both hand and foot tapping ability is reduced in both MS groups compared to controls. Interestingly, foot tapping ability was also reduced in the progressive compared to the non-progressive group with MS. Dr. Van Emmerik's team also studied the separate movement phases which make up the tapping motion, namely the up-movement ("gravity-resisting") and down-movement ("gravity-assisted"). This analysis showed increased variability in both MS groups compared to controls for up-movement in the foot but not the hand. There were no differences between MS subtypes, while foot velocity was decreased in the PMS group compared to controls in both movement phases. Overall, these results show that foot-tapping, but not hand-tapping, may be more sensitive in differentiating MS patients from controls but also the different MS subtypes.

Developing these methods will enable the researchers to advance the current knowledge of the sensorimotor function changes in people with PMS and how they relate to those diagnosed with RRMS (non-progressive) MS.

"I am grateful for the work that is being done by the scientific community on behalf of those who suffer from MS. It is truly gratifying to see the efforts that are being put forth to find ways to lessen the impact of the disease. Having served in MSRP as a consumer reviewer has given me an appreciation to the health care professional and scientists for their dedication to the research and efforts to finding a cure for MS."

Ed Tinoco, Paralyzed Veterans of America, FY19 MSRP Consumer Peer Reviewer

"The MS community is vast: patients, clinicians, caregivers, foundations, volunteers, physical therapists, MSRP, etc. Before a cure is found we need to push forward with research for innovative treatments and continue supporting programs that disrupt isolation and despair. Efforts to change the course of the disease are somewhat effective, but as with all patients with a chronic disease, I hope there will be more and better interventions for MS sooner rather than later. CDMRP is helping to drive this innovation."

Tina Rosenthal, National Multiple Sclerosis Society, FY19 MSRP Consumer Peer Reviewer

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**

"The exposure to NF research that my role as a consumer reviewer has given me has been very helpful in maintaining my hope for improvements in treatment options for my daughter and has also alerted me to the great potential of NF-related research to also benefit other research involving treatment of tumors."
Vito Grasso, NFRP Consumer Peer Reviewer

Program History

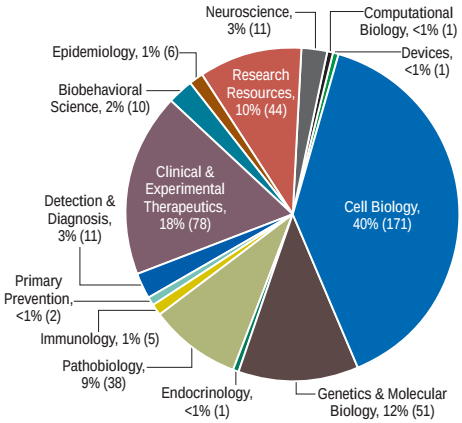
The Peer Reviewed Neurofibromatosis Research Program (NFRP) was established in FY96 when the efforts of NF advocates led to a congressional appropriation of $8M. Since that time, $362.85M has been appropriated to the program, including $15M in FY20. Over its 20-year history, the NFRP has invested in key initiatives to support the development of critical resources, sponsor multidisciplinary collaborations, bring talented investigators into the field, and promote the translation of promising ideas into the clinic. The program's research portfolio includes 409 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 Military Health System; 44% of these cases were predominately family members of active and reserve component Service members.[1] In addition, from 2009-2018 there were 6,609 DOD beneficiaries who had outpatient or inpatient encounters totaling 15,389 hospital bed days.[1] NFRP-supported research is paving the way to finding treatments for individuals with NF that impact military Service members, Veterans, and their beneficiaries.

Areas of Emphasis

Each year, the NFRP Programmatic Panel identifies and recommends research gaps and research areas of particular importance to the program, and these are highlighted as Areas of Emphasis in the program announcements. The FY20 NFRP strongly encourages research applications that specifically address the critical needs of the NF community in one or more of the following:



NFRP FY96-FY19 Portfolio Investment by SCS code (Number of Awards)

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

[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 Military Health System.

Research Accomplishments

Clinical Trials Address Quality of Life for Persons with Neurofibromatosis (NF1, NF2, and Schwannomatosis) with Resiliency Training Delivered via Live Video

Dr. Ana-Maria Vranceanu, Director, Integrated Brain Health Clinical and Research Program, Massachusetts General Hospital

The NFRP has funded two studies aimed at increasing quality of life for adults and adolescents with NF1, NF2, and Schwannomatosis. Dr. Ana-Maria Vranceanu and her team have developed stress and symptom management mind-body programs, and is examining how each program may help improve physical health and psychological quality of life in patients with NF, as well as depression, anxiety, pain, and coping ability. Recognizing that needs in various age groups can be quite different, the programs for adolescents are tailored to the needs of these young participants. The programs are delivered via secure videoconferencing, allowing easier access for patients and participation of geographically diverse persons with NF within the United States and around the world. Should these resiliency programs demonstrate improvement in quality of life, Dr. Vranceanu plans to partner with NF foundations and clinics to implement their usage.

Study Finds That Bevacizumab Treatment for NF2-Related Vestibular Schwannomas Increases Reported Quality of Life in Adults and Children Neurofibromatosis Clinical Trials Consortium

Scott Plotkin, M.D., Ph.D., Massachusetts General Hospital, and Matthias Karajannis, M.D., M.S., New York University, the first and corresponding authors on the publication describing the study

The Neurofibromatosis Clinical Trials Consortium (NFCTC) was established to develop and perform Phase I and II clinical trials for the management and treatment of NF complications in children and adults. The NFCTC researchers, led by study chair Dr. Scott Plotkin, recently published results from a Phase II evaluation of high-dose bevacizumab used as a therapy in NF2 patients with vestibular schwannomas (VSs) in the *Journal of Clinical Oncology*. The researchers enrolled children and adults with progressive VSs who were poor candidates for surgery or radiation treatment, and they evaluated the hearing response and radiographic response rates to the medication. When compared to lower doses, high-dose bevacizumab seemed to be similarly effective at increasing hearing response and shrinking tumors, suggesting that the lower doses are adequate for treatment. Both adults and children reported improvements in quality of life, which indicates that treatments incorporating bevacizumab could be beneficial to children with NF2. Over the years, the NFCTC has expanded from 9 to 15 primary sites with an additional 9 affiliate sites. Since the development awards offered in FY05, the NFCTC has been supported by additional awards from the NFRP in FY06, FY11, and FY16.

Bench to Bedside – Collaborating to Develop Effective Therapies for NF

The funding efforts of the four major federal and philanthropic organizations for NF1, including CDMRP, Children's Tumor Foundation, NIH, and Neurofibromatosis Therapeutic Acceleration Program at Johns Hopkins University, have played a crucial role in accelerating the advancement of MEK inhibitors to human clinical trials for NF1-associated tumors and to the eventual FDA approval of Selumetinib, the first drug for the treatment of symptomatic, inoperable plexiform neurofibromas. The NFRP has been a critical partner in moving the field of NF research from understanding the basic biology of the disorder to identifying potential therapeutics and testing in clinical trials. The NFRP has funded several clinical trials that use MEK inhibitors to target manifestations of NF1, including low-grade gliomas, plexiform neurofibromas, and malignant peripheral nerve sheath tumors; three are currently enrolling new patients. For more information on specific NFRP trials, visit https://cdmrp.army.mil/nfrp/clinical_trials/nf1.

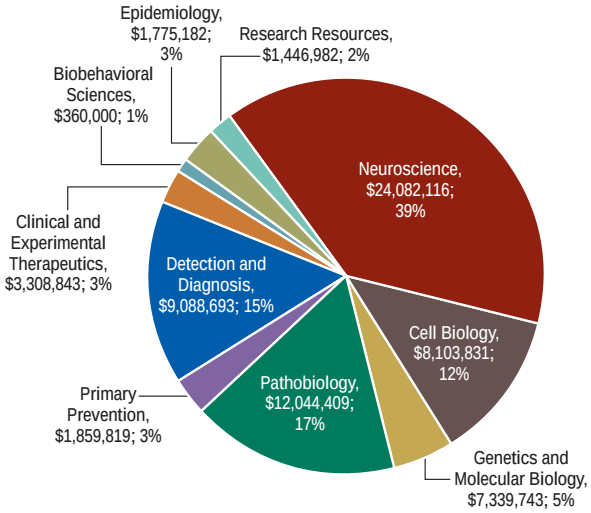
NEUROTOXIN EXPOSURE TREATMENT PARKINSON'S

Program History

The Peer Reviewed Neurotoxin Exposure Treatment Parkinson's (NETP) program was initiated in FY97 to provide support for research of exceptional scientific merit leading to an understanding of the cause, prevention, and treatment of Parkinson's disease (PD) in the context of neurotoxin exposure.

The vision of the NETP program is to eliminate PD through neurotoxin exposure and treatment-related research in partnership with scientists and consumers.

The NETP program invests in scientific research to better understand and treat the neuro-degenerative effects of PD associated with military deployment, environmental, and/or occupational exposures. Research into military service-related risk factors is critical for past, present, and future Service members who may be affected PD.



FY15-FY19 NETP Portfolio Investment by SCS Code

Appropriations for the NETP Program from FY97 through FY19 totaled $452.75M. The FY20 appropriation is $16M.

Military Relevance

The VA estimates that PD affects more than 80,000 Veterans, which is a higher proportion than that of the general population. A preliminary study[1] found that military deployment is associated with a 1.8-fold increased risk of PD. In 2010, the VA recognized PD as associated with exposure to Agent Orange or other herbicides during military service.[2] Peer-reviewed studies have identified several risk factors for the development of PD that are related to military deployment and service. The most significant factors are:

- Exposure to chemicals with potential neurotoxic effects (including pesticides, insecticides, and solvents)
- Traumatic injury to the head
- Depression
- Prolonged physiological and mental stress
- Repeated or prolonged disruption of sleep architecture
- Repeated or prolonged disruption of autonomic nervous function

The NETP invests in scientific research to better understand and treat the neuro-degenerative effects of PD associated with military deployment, environmental, and occupational exposures.

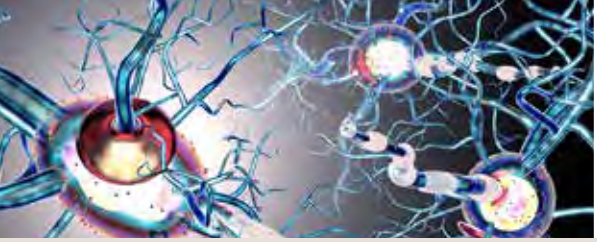
[1] Lorene Nelson, Ph.D., MS; Stanford University School of Medicine, Stanford, CA 94305; "Military Service and Parkinson's Disease" (W81XWH1110258).

[2] A Rule by the Veterans Affairs Department on 08/31/2010; Diseases Associated With Exposure to Certain Herbicide Agents (Hairy Cell Leukemia and Other Chronic B-Cell Leukemias, Parkinson's Disease and Ischemic Heart Disease).

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

Mission: **Support Parkinson's research investigating the underlying biologic mechanisms and therapeutic interventions of neuro-degenerative effects caused by deployment, environmental, and occupational exposures in Service members and Veterans**

"...I can personally attest to the impact of financing this research. The care, depth, and innovation the panel undertakes in targeting studies to impact specific disease composition, is truly amazing. I am proud of the entire team's commitment to help current and past Service members, their families and fellow patients battle this horrible disease."
Kelly Sweeney, Parkinson's Resources of Oregon, NETP Consumer Reviewer



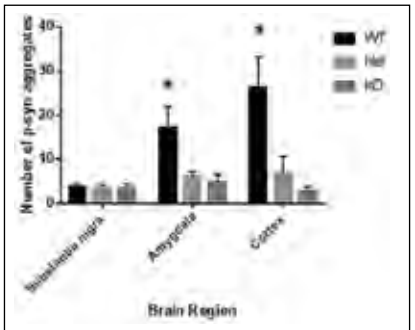
Research Accomplishments

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

Laura A. Volpicelli-Daley, Ph.D., University of Alabama 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 that 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 University of Alabama 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.



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

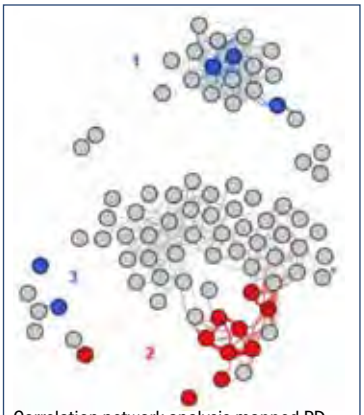
Findings from Dr. Volpicelli-Daley's study and additional published research suggests that reducing tau prevents the formation of fibril-induced alpha-synuclein inclusions and improves behavioral tests of cognition.

"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."
Laura A. Volpicelli-Daley, Ph.D., University of Alabama Birmingham

Identifying an Additional Risk for Sporadic Parkinson's Disease in the Gut Microbiome

Haydeh Payami, Ph.D., University of Alabama Birmingham

It is known that the identified genetic and environmental risk factors for development of sporadic PD are not sufficient to explain development of the condition. It is therefore important to identify other risks that impact disease development. Dr. Haydeh Payami and Dr. David Standaert at the University of Alabama, Birmingham are investigating the effect of changes in the gut microbiome on PD risk in partnered studies funded through CDMRP's Parkinson's portfolio (awards W81XWH1810508 and W81XWH1810509), title: "Interactions of Gut Microbiome, Genetic Susceptibility, and Environmental Factors in Parkinson's Disease." Prior studies indicated that the microbiome, i.e., the population of microorganisms that inhabit the intestine, influence both health and disease. Studies also show that the gut microbiome in PD patients is different from that in non-PD individuals. Three clusters of microorganisms have been identified in persons with PD: increased opportunistic pathogens, reduced numbers of microbes that produce short-chain fatty acids, and increased numbers of carbohydrate-metabolyzing probiotic microbes. The association of the altered microbiome with PD patients is not proof of a mechanistic effect of the microbiome changes and PD risk, but it is an important area of investigation. The intent of the current study is to determine the role and mechanism of an altered microbiome on PD risk and development. More specifically Drs. Payami and Standaert intend to identify the specific species altered in postural instability, freezing of gait, and treatment-associated dystonia. Success in the project will provide not only important information on the risk for development of PD from deleterious changes in the gut microbiome, but may also provide new PD treatments.



Correlation network analysis mapped PD-associated genera to three polymicrobial clusters shown in gray, and the 15 PD-associated genera highlighted in blue (if increased in PD) or red (if decreased in PD).[1]

[1] Wallen ZD, Appah M, Dean MN, et al. 2020. Characterizing dysbiosis of gut microbiome in PD: Evidence for overabundance of opportunistic pathogens. *npj Parkinson's Disease*. 6:11. https://rdcu.be/b4Vrw.

ORTHOTICS AND PROSTHETICS OUTCOMES RESEARCH PROGRAM

Program History

Limb deficit is one of the most debilitating traumatic injuries suffered by US military personnel. Recent advancements in commercially available orthotics and prosthetics have dramatically improved device capability; however, there remains an urgent need for continued development of devices, associated rehabilitation treatments, and an evidentiary basis for their prescription and use to provide improved quality of life for our Service members.

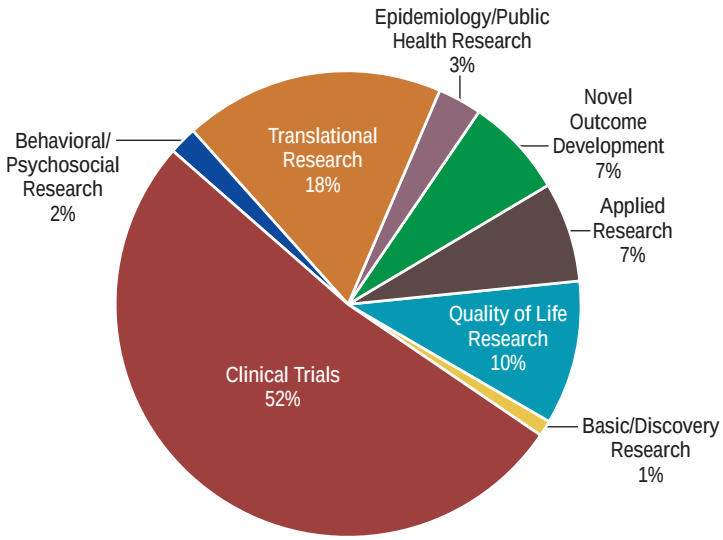
The Orthotics and Prosthetics Outcomes Research Program (OPORP), was established by Congress in FY14 to support military-relevant personal assistive technology outcomes research. The program seeks to improve rehabilitation and reintegration strategies for wounded Service members, replace the function of injured limbs, prevent and mitigate the secondary health effects of neuromusculoskeletal injuries, and support validated metrics for rehabilitation and reintegration after injury. The goal of the OPORP is to improve our understanding and ultimately advance the implementation of the most effective prescriptions for prosthetic and orthotic devices, treatment, rehabilitation, and secondary health effect prevention options for patients, clinicians, other caregivers, and policy makers.

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

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

"Serving as a consumer peer reviewer for CDMRP has been a challenging and rewarding experience. Challenging to read and learn the science but greatly rewarding to fund good research. Working with experts in their fields but being able to bring the patient's experience to the process is very fulfilling. It is exciting to be able to help fund research and clinical trials that will directly impact people."
William Keating, OPORP Consumer Reviewer

"I believe the greatest influence the OPORP has is its ability to fund meaningful research and timely clinical trials that directly impact the lives of our Service members and advance the profession of orthotics and prosthetics."
Mark Muller CPO, FAAOP, MS, California State University, OPORP Programmatic Panel Member



FY14-FY19 OPORP Portfolio Investment by SCS Code
$54,638,434 in 56 awards

Research Highlights

Needs, Preferences, and Functional Abilities of Veterans and Service Members with Upper-Limb Amputation

Linda Resnik, P.T., Ph.D., FAPTA, Providence VA Medical Center

As the recipient of a FY15 Prosthetics Outcomes Research – Funding Level 2 Award, Dr. Linda Resnik and her collaborators are conducting a study to provide comprehensive cross-sectional and longitudinal data on function, needs, preferences, and satisfaction of Veterans and Service members living with major upper limb amputation. Over the last decade, the VA has focused on improving the care of Veterans with amputation, including the re-organization of its amputation system of care in 2009 and the release of VA and DOD evidence-based Clinical Practice Guidelines for rehabilitation of individuals with upper limb amputation. Dr. Resnik's work is assessing the current state of quality and outcomes of amputation care as well as the impact of the newly implemented guidelines.

Methods and summary findings for the study team's initial work were published in PLOS ONE and focus on their assessment of the quality and outcomes of care of Veterans with upper limb amputation.[1] In total, there were 808 survey respondents, including 776 unilateral amputees and 32 bilateral amputees. Notably, this was the first ever nationally representative study of Veterans with all cause upper limb amputation. As part of this assessment, the study team found that rates of prosthesis use in the study populations were lower than previously reported for combat Veterans. In addition, a substantial proportion of amputees never received prosthetic training to use either their initial or current prostheses. Veterans with upper limb amputation were found to have moderately impaired physical functioning and musculoskeletal problems, with phantom limb and residual limb pain affecting the majority. Through this initial assessment and their other research, this study is yielding important new knowledge and findings with potential to inform evidence-based policies and provide insights that may allow for the improvement of VA and DOD quality of care for individuals with upper limb amputation.

[1] Resnik L, Ekerholm S, Borgia M, and Clark MA. 2019. A national study of Veterans with major upper limb amputation: Survey methods, participants, and summary findings. *PloS One*, 14(3), e0213578.

Women's Specific Footwear with Prosthetic Feet

Elizabeth Russell Esposito, Ph.D., DOD-VA Extremity Trauma and Amputation Center of Excellence (EACE), VA Puget Sound

Dr. Elizabeth Russell Esposito's research focuses not only on the device we put onto the person, but also the person we put into the device. As the recipient of a FY16 Prosthetics Outcomes Research – Funding Level 1 Award, Dr. Russell Esposito and her team from the Minneapolis VA, Northwestern University, and Shirley Ryan Ability Lab are characterizing perceived limitations in footwear among women prosthesis users, using a survey distributed to a nationwide sample of women Veteran and Service member prosthesis users. They are also comparing how different styles of women's footwear may change the mechanical properties of various adjustable heel-height prosthetic feet.

Having the choice to wear desired footwear or footwear deemed appropriate for a given occasion is an important part of community reintegration following lower limb amputation. The preliminary data confirm previously anecdotal reports of challenges and limitations for women prosthesis users in terms of footwear able to be worn and desired to be worn. Women want to be able to wear a greater variety of footwear than they currently do, which may contribute to the greater dissatisfaction previously reported in women prosthesis users compared to their male counterparts. Over 50% of respondents "agreed" or "strongly agreed" that the width, height, and shape of their prosthetic foot made it difficult to fit in shoes. Of note, over half of the survey respondents indicated wearing high heeled shoes at least monthly or more often prior to amputation. However, not one person indicated wearing them at all post-amputation despite 23% of respondents reporting high heels as "moderately," "very," and "extremely" important to wear.

The survey that was distributed to women prosthesis users covers much more than footwear; it also examines mobility, body image, balance confidence, community participation, and quality of life. This project was recently awarded additional funding from JPC 8/ Clinical and Rehabilitative Medicine Research Program to compare responses from women to an existing data set on over 200 men with lower limb amputations that study team member Dr. Christopher Erbes from the Minneapolis VA previously collected. Support of this analysis will provide a broad-ranging analysis and characterization of factors that affect quality of life that women experience relative to men after a lower limb amputation.

OVARIAN CANCER RESEARCH PROGRAM

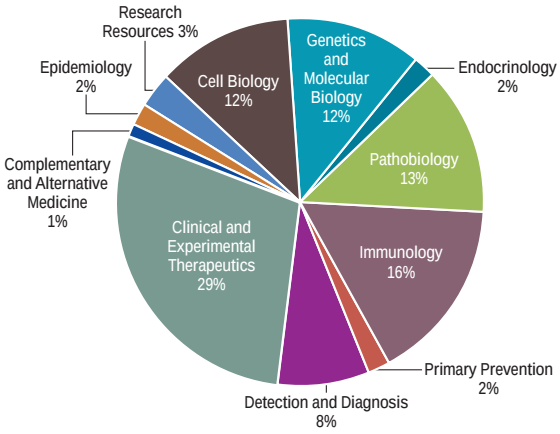
Program History

The DOD Peer Reviewed 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-FY20, the OCRP has received $371.5M in congressional appropriations and is the second-leading funder of ovarian cancer research in the US. Through FY19, the OCRP has funded 479 research awards, resulting in over 1,871 peer-reviewed publications and 112 patent applications. The appropriation for OCRP for FY20 is $35M.

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

Program Portfolio

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



FY15-FY19 OCRP Portfolio Investment by SCS Code

High-Impact Research Supported by the OCRP

Prevention

- More precise risk assessment with mutations in non-BRCA genes
- Genetic testing guidelines in the US and Australia
- Salpingectomy as a less invasive alternative surgery

Detection

- A blood-based assay for non-invasive early detection
- Falloposcope system to identify ovarian cancer
- Adapting pap smears to detect ovarian cancer

Survivorship

- Self-administered relaxing acupuncture to reduce fatigue
- Initiated two consortia focused on long-term survivorship

Treatment

- The benefits of aspirin in improving patient outcomes
- Junctional opener 1 triggers the opening of cells and allows more effective treatment
- Utilizing heat shock protein inhibitor in combination with PARP inhibitor in recurrent ovarian cancer

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**

"I see firsthand that consumers' perspectives are important and they add a significant component to the entire process. Serving on first the peer and then the programmatic review panels has been an incredible experience. I am convinced that the OCRP currently and will continue to provide the research base from which more effective treatments and eventually a cure for ovarian cancer will be developed."
Debbie Miller, OCRP Consumer Reviewer

Funding Research with Direct Military Impact

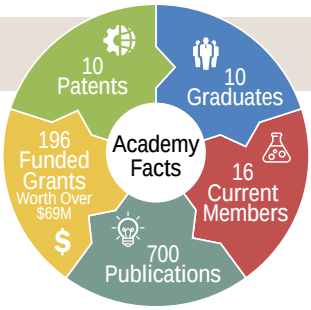
Elizabeth Swisher, M.D., University of Washington and Scott Kaufman, M.D., Ph.D., Mayo Clinic

The OCRP awarded Drs. Elizabeth Swisher and Scott Kaufman a Synergistic Translational Leverage Award to support laboratory work associated with a Phase 2 clinical trial that led to the FDA-accelerated approval for oral therapy rucaparib (Rubraca, Clovis Oncology) for the treatment of advanced ovarian cancer with BRCA1 or BRCA2 mutations. This therapy is currently used to treat Service members. In 2017-2018, 126 rucaparib prescriptions were in the Military Health System.[1]

Laura Kubzansky, Ph.D., Harvard T. H. Chan School of Public Health

Dr. Laura Kubzansky and colleagues predicted that PTSD might cause an increased risk of ovarian cancer. With OCRP support Dr. Kubzansky explored this potential link between PTSD and ovarian cancer. Leveraging existing data from the Nurses' Health Study II, which included over 50,000 women followed for 25+ years with detailed assessments on PTSD, the team also monitored ovarian cancer development and survival. Women with high PTSD symptoms had a twofold greater risk of ovarian cancer versus women with no trauma exposure. They determined that PTSD is associated with increased ovarian cancer risk, particularly in premenopausal women. In addition, the study found PTSD was associated with the most aggressive forms of ovarian cancer.

Ovarian Cancer Academy: FY20-FY25 Deans



Since its inception in FY09, the Ovarian Cancer Academy has become a successful career development platform where highly committed Early-Career Investigators (ECIs), their mentors, the Academy Dean, and the Assistant Dean diligently collaborate and network as they work toward becoming the next generation of leaders in ovarian cancer research.

The Ovarian Cancer Academy Leadership Award was awarded in FY19 and will begin in 2020. Drs. Nita Maihle and Douglas Levine will continue to serve as the FY20-FY25 Dean and Assistant Dean, respectively. Their vision for the Academy focuses on four major areas: assisting Academy ECIs (1) to work smarter – not harder, (2) appreciate the value of inclusivity in the research process, and (3) value the contributions of patient advocates, as well as (4) to conduct evaluations on the effectiveness of the Academy. The program values the continued leadership of the OCRP Academy by Drs. Maihle and Levine and their commitment to developing outstanding leaders in ovarian cancer.

Funding New Therapeutics in Ovarian Cancer

Ronald Buckanovich M.D., Ph.D., Magee-Womens Hospital

Dr. Ronald Buckanovich identified that NFAT3 activation is associated with ovarian cancer chemotherapy resistance. He determined that NFAT3 induces expression of CDK6 and demonstrated that the CDK4/6 inhibitor, LEE011, induces a partial growth arrest in ovarian cancer cells. He also determined that a combination of CDK4/6 inhibitor and chemotherapy is highly synergistic and effective in ovarian cancer. A Phase I clinical trial of Ribociclib (LEE-011) with chemotherapy in recurrent platinum-sensitive ovarian cancer derived from these studies has now completed accrual after enrolling 35 patients and will have mature data later this year. Further studies have identified additional NFAT mediated drivers of chemotherapy resistance as new therapeutic targets.

Danuta Kozbor, Ph.D., Health Research, Inc., Roswell Park Division

Dr. Daunata Kozbor explored the use of an antagonist to the chemokine receptor CXCR4 as an adjuvant during ovarian cancer treatment. CXCR4 antagonists are known to have anti-tumoral effects, but CXCR4 is widely expressed, making side effects a concern. Her team utilized locoregional delivery of a CXCR4-armed oncolytic virus that reduced the tumor size as well as immunosuppression in the tumor microenvironment. This permitted infiltration of immune cells capable of providing long-term control of tumor growth. This study reveals a viable approach for in situ vaccination to bolster the anti-tumor immune responses.

[1] Data provided by the Defense Health Agency, Pharmacy Analytics Support Section.

PANCREATIC CANCER RESEARCH PROGRAM

Vision: **A diminished burden of pancreatic cancer among Service members, Veterans, their families, and the American public**

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

Pancreatic Cancer and PCARP History:

Based on data from the National Cancer Institute, there were an estimated 56,770 new cases of pancreatic cancer diagnosed in the United States during 2019. Pancreatic cancer is also the eleventh most common type of cancer in the United States, representing 3.2% of all new cancer diagnoses every year. The 5-year survival rate for those with pancreatic cancer is just over 9%. Since 2011, the CDMRP has funded pancreatic cancer research through the Peer Reviewed Cancer Research Program (PRCRP). From FY11 through FY18, the PRCRP invested over $23M in pancreatic cancer research.

For FY20, the United States Congress established the Peer Reviewed Pancreatic Cancer Research Program (PCARP) in the DOD appropriation with an appropriation of $6M. Program Announcements to be solicited for FY20 are the Idea Development Award and Translational Research Partnership Award. The Idea Development Award will have a single PI option, as well as a partnering PI option, which includes an early-career investigator. With this new 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.

"The establishment of the CDMRP PCARP is a vote of confidence by Congress on the critical importance of reducing the burden of pancreatic cancer in our society, especially amongst active duty personnel, Veterans, and their family members. I am hopeful that it will bring together a united front of clinicians and researchers pursuing the most innovative science geared toward newer treatments and early detection strategies against this disease."

Anirban Maitra M.B.B.S., M.D., PCARP Programmatic Panel Chair

"My hopes are high with enthusiasm for the PCARP program in accelerating possibilities of eliminating needed gaps in the pancreatic cancer research scenario and providing knowledge and information to extend patient quality of life to enhance the survivorship for ALL affected by this horribly devastating cancer."

Kay Kays, PCARP Programmatic Panel Member/ Pancreatic Cancer Survivor

FY20 PCARP Focus Areas

During the FY20 Vision Setting meeting, the Programmatic Panel decided on the following list of Focus Areas that applicants need to address:

- 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
- Integration of biologic and imaging biomarkers to drive more precise and earlier detection and prognosis
- Defining viable tumor burden
- Supportive care and patient reported outcomes, quality of life, and perspectives during treatment and survivorship
- New drug development targeted toward cancer sensitivity and resistance mechanisms, including immune mechanisms of resistance
- Development of pharmacological, immunological, or genetic interception approaches

PCARP Funding Opportunities for FY20

Award Mechanism	Key Elements
Idea Development Award with Early-Career Investigator Option	Supports new ideas that represent innovative, high-risk/high-gain approaches to pancreatic cancer research and have the potential to make an important contribution to one or more of the FY20 PCARP Focus Areas. Early-Career Investigator Option will support researchers early in their faculty appointments to promote his/her career development in pancreatic cancer research.
Translational Research Partnership Award	Supports partnerships between clinicians and laboratory scientists that accelerate ideas in pancreatic cancer into clinical applications.

PEER REVIEWED ALZHEIMER'S RESEARCH PROGRAM

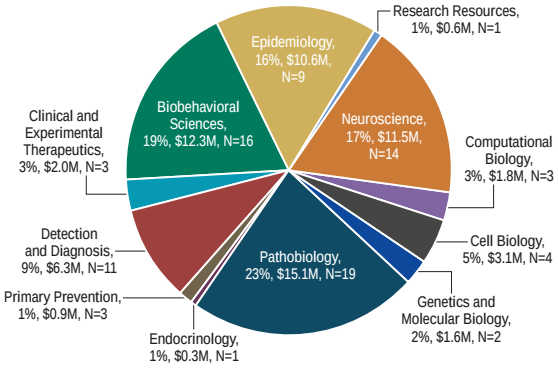
Vision: **To address the long-term consequences of traumatic brain injury as they pertain to Alzheimer's disease and Alzheimer's disease-related dementias**

Mission: **The PRARP's mission is devoted to understanding the association between traumatic brain injury and Alzheimer's disease/Alzheimer's disease-related dementias, and to reducing the burden on affected individuals and caregivers, especially in the military and Veteran communities**

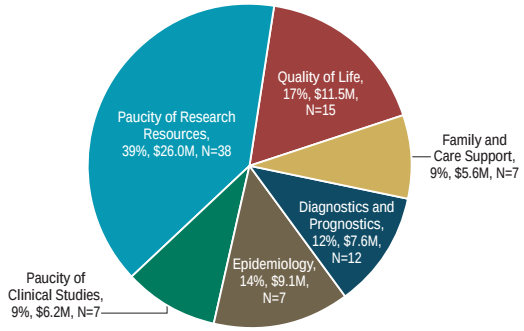
"As a Consumer Peer Reviewer, I was proud and excited to be a part of the PRARP funding program for vital research. My distinguished scientific teammates made obvious an appreciation and respect of my role in providing insight into the real-life applications of the research science that has the potential to impact the lives of those directly affected by Alzheimer's and related dementias."
Dorian Bannister, PRARP Consumer Peer Reviewer

Program History

The DOD Peer Reviewed Alzheimer's Research Program (PRARP) was established in FY11 to address the long-term consequences of TBI as they pertain to AD and AD-related dementias (ADRD) in civilian and military communities. Military personnel and other individuals living with TBI face an increased risk for developing dementia, aggression, memory loss, depression, and symptoms similar to those of other neurological diseases. The PRARP has funded over 120 research projects since its inception in FY11, ranging in topics from TBI-ADRD pathology to quality of life for individuals living with cognitive impairments. Each year, the PRARP Programmatic Panel sets its Overarching Challenges, which represent long-standing research goals for the program. The Overarching Challenges support innovative and impactful research.



FY15-FY19 PRARP Portfolio Investment by SCS Code



FY15-FY19 PRARP Overarching Challenge Investments

Overarching Challenges

- **Foundational Research:** Research to examine the interrelationship between TBI and subsequent AD/ADRD for the military, Veteran, and civilian communities and to translate these findings.
- **Paucity of Clinical Studies:** The paucity of clinical studies to examine the interrelationship between TBI and subsequent AD/ADRD for the military, Veteran, and civilian communities.
- **Diagnostics and Prognostics:** The need for technologies, tests, surveys, questionnaires, devices, biomarkers, or analyses to detect TBI sequelae for AD/ADRD utilizing new and/or pre-existing datasets.
- **Epidemiology:** The paucity of epidemiological research to examine the interrelationship between TBI, risk and resiliency factors, and subsequent AD/ADRD for the military, Veteran, and civilian communities.
- **Quality of Life:** The need for technologies, assessments, interventions, or devices to benefit individuals living with the common symptoms of TBI and AD/ADRD.
- **Family and Care Support:** The need for technologies, assessments, interventions, or devices that enhance the lives of those providing care and families of individuals living with the common symptoms of TBI and/or AD/ADRD.

Research Highlights

Understanding Long-Term TBI Consequences Using Artificial Intelligence

Duygu Tosun-Turgut, Ph.D., Northern California Institute for Research and Education, US Department of Veterans Affairs, San Francisco VA Healthcare System, and University of California San Francisco

The long-term risks of head injuries are poorly understood, with some studies suggesting severe consequences and others no consequence at all. Two major challenges exist when trying to understand the long-term nature of TBIs. First is the lack of large and well-characterized datasets. Large datasets reveal how TBIs exert long-term effects across a population that is truly representative of individuals who experience a TBI. Injuries also need to be well characterized in terms of severity, age of injury, and the overall health of the individual at the time of injury. The second major challenge is finding high quality, objective data like medical images or blood tests that can tell us more about the biological nature of an individual TBI. When biology and data science are combined, a precise prognosis can be made within a given population.

These two challenges each separately represent daunting tasks, and combining them into a single study would seem to be impossible. Information technologies, such as artificial intelligence, now make bringing together and analyzing large, disparate types of data feasible. Dr. Duygu Tosun-Turgut is working with a large dataset that includes MRI data of more than 1.6 million Veterans with and without a TBI. As the MRI data from these Veterans is verified and processed, it will be used to test an algorithm that can predict 5+ year risk of developing post-TBI dementia. Dr. Tosun-Turgut anticipates building a database of 200,000 patient records with as many as 12,000 structural MRIs used to inform the algorithm. The algorithm may predict a dementia or another outcome based on MRI data years before signs of cognitive decline. Understanding TBI-dementia at its earliest stages may lead to improved study designs for future clinical trials.

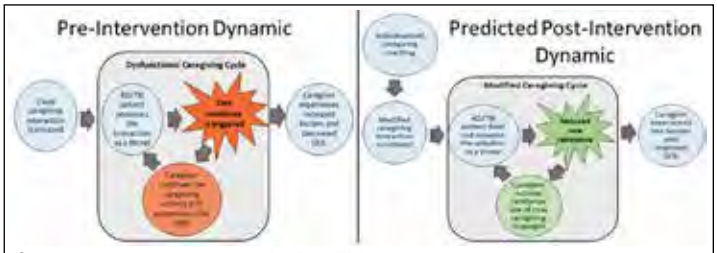
TBI-associated cognitive impairments may present with unique tissue atrophy signatures as shown in brain modeling from MRI

Improving Quality of Life Through Training to Reduce Care-Resistant Behaviors

David Geldmacher, M.D., University of Alabama at Birmingham

Caring for individuals who live with a neurological impairment such as TBI or AD/ADRD can be challenging. Caregivers must show compassion for individuals with a variety of symptoms that can include memory issues, poor judgement, and depression. Quite often, a caregiver is faced with the challenge of helping an individual eat, get dressed, or shower. That individual may refuse their help, and may be unable to complete that activity. This leads to a declining state of health for not only the person with the impairment, but the caregiver as well. Tools and strategies that enable a caregiver to deal with these significant challenges are truly needed.

Dr. David Geldmacher has developed a strategy that prepares caregivers for encounters with care-resistant behaviors. Dr. Geldmacher's approach involved six weekly online coaching sessions conducted by a nurse practitioner. These helped participants set goals for improving how they interact with their family member. The sessions were tailored to individual needs, since the personal history of the person affected by the neurological impairments was a factor in the overall intervention. The coaching involved role-playing and script development to guide the caregiver when confronted with a care challenge at home. Using the combination of education, role-playing, and custom-tailoring, the training has shown some success in a small cohort of participants funded by the PRARP; the study is currently ongoing.[1] While study outcomes have thus far focused on individuals living with dementia, it also tests this coaching approach for caregivers for those living with TBI.



Cognitive losses in people with AD or TBI may cause them to perceive caregiving activities as physical or psychological threats. This results in a dysfunctional cycle of resisting care that can increase caregiver burden and decrease quality of life in the family setting. This project coaches caregivers to use individualized strategies to change their approach to care activities, with the intent to trigger less care-resistant behavior. A successful intervention would result in reduced caregiver burden and improved quality of life for the family.

[1] Jablonski R, Winstead V, and Geldmacher D. 2019. Description of process and content of online dementia coaching for family caregivers of persons with dementia. *Healthcare (Basel)* 7(1):13. doi: 10.3390/healthcare7010013.

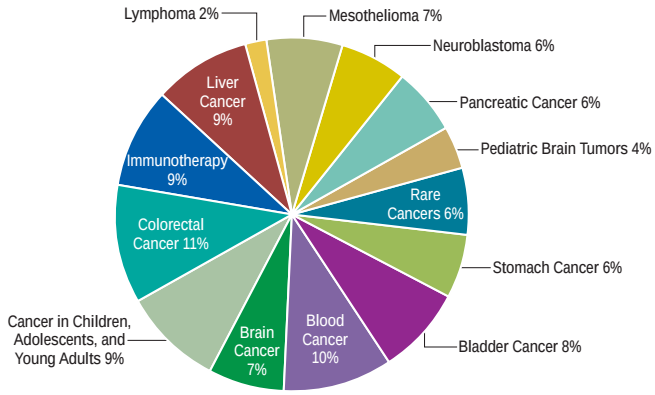
PEER REVIEWED CANCER RESEARCH PROGRAM

Program History

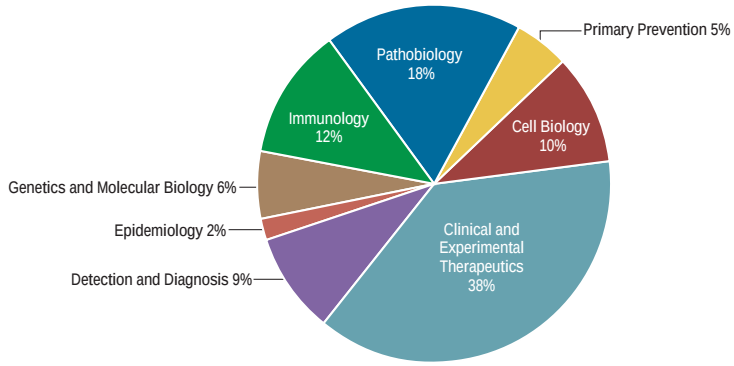
The Peer Reviewed Cancer Research Program (PRCRP) was established in FY09 to support innovative research in cancers and other specialty areas designated by Congress. From FY09 through FY20, Congress has appropriated $539.8M to PRCRP, which in turn has invested in cancer research covering 28 topic areas.* PRCRP-funded research has advanced knowledge on the prevention, early detection, diagnosis, and treatment of cancer that benefits Service members, their families, Veterans, and the American public. The PRCRP's investment strategy focuses on military health concerns, especially how cancer affects mission readiness. All applications submitted to and funded by the PRCRP must show relevance to military health. In FY20, there are two military health Focus Areas.

FY20 PRCRP Military Health Focus Areas

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



FY19 PRCRP Portfolio Investment by Topic Area (% Research Dollars)



FY09-FY19 PRCRP Portfolio Investment by SCS Code* (% Research Dollars)

*As of publication the FY20 applications were under review.

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

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

"The PRCRP offers an incredible opportunity for scientists to fund their innovative cancer research projects. The PRCRP's grant portfolio is composed of several award mechanisms designated for new investigators, mid-career scientists, and well-established investigators. With an emphasis in innovation and impact, the PRCRP's goal is to fill gaps in current cancer research to bring novel ideas from the bench to the bedside, which will both improve cancer care and survivorship for our military active duty, Veterans, their families, and all Americans"
Col Thomas Newton, FY20 Programmatic Panel Member

PRCRP Funded Research Through the Cancer Care Spectrum

Biology/Etiology	
Topic Area: **Mesothelioma**	 ***Richard Lake, Ph.D., University of Western Australia*** **The MexTAg Collaborative Cross: Understanding Genetic Modifiers in Mesothelioma** Dr. Lake's research team aims to identify genes that promote or protect against mesothelioma. Using a new mouse model, the team will investigate how mesothelioma develops after exposure to asbestos, looking specifically at genes involved in the progression of mesothelioma.
Prevention	
Topic Area: **Cancer in Children, Adolescents, and Young adults**	 ***Carri Geer, Ph.D., Novan Inc.*** **Topical Nitric Oxide Therapy to Treat Cervical Neoplasias and Prevent HPV Associated Cancers** The team at Novan Inc. is developing an antiviral vaginal suppository that can be self administered as a potential treatment for cervical intraepithelial neoplasia that aims to eradicate latent human papillomavirus (HPV) infection and inhibit disease progression to cancer.
Diagnosis/Detection	
Topic Area: **Bladder Cancer**	 ***James McGrath, Ph.D., University of Rochester*** **Nanomembrane Capture and Characterization of Cancer-Derived Exosomes in Urine** Dr. McGrath's team is developing a novel nanomembrane microdevice platform that captures exosomes from a small volume of urine as a source for diagnostic bladder cancer biomarkers.
Topic Area: **Colorectal Cancer**	 ***Viktor Gruev, Ph.D., University of Illinois*** **Bioinspired Color and Near-Infrared Endoscopy with Affibody Targeted Markers for Colorectal Cancer Surgery** Dr. Gruev and his team are developing a multispectral color near-infared endoscope for screening colonoscopy in the high-risk inflammatory bowel disease patient population, with special emphasis on detecting flat lesions of colitis-associated cancer/dysplasia and distinguishing benign from malignant polyps in both civilian and military populations.
Prognosis	
Topic Area: **Stomach Cancer**	 ***Ju-Seog Lee, Ph.D., MD Anderson*** **Marker-Based Targeting of Chemoresistant Subtype of Gastric Cancer Discovered by Proteomics** Dr. Lee identified a set of genes to predict patients at high risk of recurrence after treatment. If validated in a prospective clinical trial cohort, the prediction model may become the foundation for marker-based treatment of gastric cancer patients.
Treatment	
Topic Area: **Lymphoma/ Blood Cancers**	 ***Larry Kwak, M.D., Ph.D., City of Hope*** **Novel CAR-T Therapy Targeting BAFF-R Against B-Cell Lymphomas** Kwak's team at City of Hope has developed and optimized a BAFF-R chimeric antigen receptor that is highly active against lymphoma cells. Further clinical manufacturing of T cell subsets is underway.
Topic Area: **Liver Cancer**	   ***Nabeel Bardeesy, Ph.D., Massachusetts General Hospital*** ***Kevan Shokat, Ph.D., UCSF*** ***Andrew Zhu, M.D., Ph.D., Massachusetts General Hospital*** **A Proteomic Co-Clinical Trial of BGJ-398 in FGFR-Driven Biliary Cancers** The multi-institutional research team performed genetic analyses of patient tumor biopsies and identified the FGFR signaling pathways and mutations driving tumor development and drug resistance in cholangiocarcinomas. Also, they discovered the FGFR inhibitor TAS-120 was effective in treating patients with advanced cholangiocarcinoma that had developed resistance to other treatments.
Survivorship	
Topic Area: **Cancer in Children, Adolescents, and Young Adults**	 ***Caitlin Murphy, M.PH., Ph.D., UT Southwestern*** **Fertility and Reproductive Outcomes of Adolescent and Young Adult Cancer Survivors in Texas** Dr. Murphy's goal is to characterize fertility and reproductive outcomes among Adolescent and Young Adult survivors of cancer and estimate the risk of birth defects in the next generation.

PEER REVIEWED MEDICAL RESEARCH PROGRAM

Program History

The Peer Reviewed Medical Research Program (PRMRP) was established in FY99 to provide support for military health-related research of exceptional scientific merit toward the goal of improving the health and well-being of military Service members, Veterans, and their family members. Through its 21-year history, Congress has appropriated $2.71B to the program, which has supported more than 1,612 research awards in 170 unique diseases and conditions, resulting in over 3,100 peer-reviewed publications and 272 patent applications and patents granted. The FY20 congressional appropriation is $360M to solicit research applications in 44 different diseases and conditions.

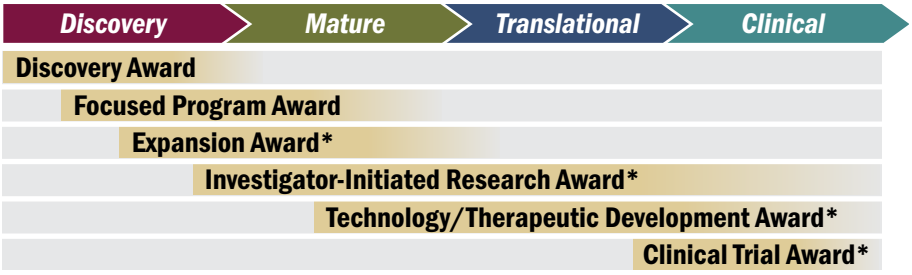
Research supported by the PRMRP to address near-term needs continues a long tradition of research relevant to military health in response to wartime needs that ultimately benefits Service members and civilians alike. Service members, their dependents, and Veterans receive military medical services, creating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

Vision: **Improve the health, care, and well-being of all Military Service members, Veterans, and beneficiaries**

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

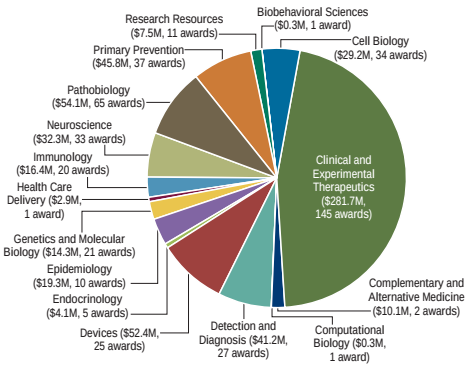
In FY20, the PRMRP released four additional program announcements specifically addressing research on COVID-19 and SARS-COV-2. Twenty-four applications were recommended for funding, representing 21 unique projects and $76.6M of the PRMRP FY20 appropriation.

FY19-FY20 PRMRP Award Mechanisms

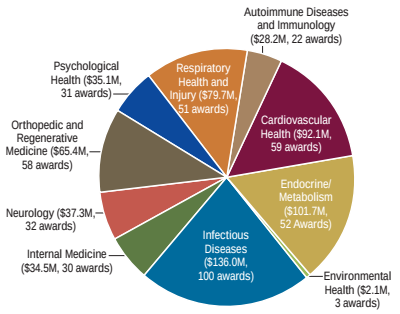


*COVID-specific Program Announcements released in FY20

The PRMRP is committed to funding research that has the potential to profoundly impact the development and implementation of medical devices, drugs, and clinical guidance that will enhance the precision and efficacy of prevention, diagnosis, and treatment across a wide range of disciplines, including autoimmune diseases and immunology, cardiovascular health, endocrine/metabolism, environmental health, infectious diseases, internal medicine, neurology, orthopaedic and regenerative medicine, psychological health, and respiratory health and injury.



FY18-FY19 PRMRP Investment by SCS Code



FY18-FY19 PRMRP Investment by Portfolio

Portfolio Highlights

Autoimmune Diseases & Immunology

FY18-FY20 Awards by Primary and Secondary Topic Areas

Food Allergies	Returning in FY20
Guillain-Barre Syndrome	FY18 (0), FY19 (2), FY20
Hereditary Angioedema	FY18 (0), FY19 (0)
Immunomonitoring of Intestinal Transplants	FY18 (3), FY19 (1), FY20
Inflammatory Bowel Diseases	FY18 (6), FY19 (5), FY20
Rheumatoid Arthritis	FY18 (1), FY19 (3), FY20
Scleroderma[1]	FY18 (0), FY19 (2)

Highlight:
Rheumatoid Arthritis

Rheumatoid arthritis (RA) continues to challenge healthcare providers and researchers because it is difficult to accurately diagnose, and there are still many questions about rheumatoid autoimmune antibodies. Citrullinated proteins, which are produced by peptidylarginine deiminases enzymes in immune cells, are targeted by some RA-associated autoimmune antibodies. Through support from the FY17 PRMRP Investigator-Initiated Research Award, Dr. Miriam Shelef is elucidating the role of peptidylarginine deiminases and citrullination in RA by studying healthy immune response compared to RA. If successful, these studies would identify a new mechanistic link between peptidylarginine deiminases, immune regulation, and autoantibody generation, potentially guiding the development of new diagnostics and therapeutic targets for RA.

Cardiovascular Health

FY18-FY20 Awards by Primary and Secondary Topic Areas

Cardiomyopathy	FY18 (15), FY19 (15)
Congenital Heart Disease	FY18 (7), FY19 (10), FY20
Hemorrhage Control	FY19 (9), FY20
Vascular Malformations	FY18 (3), FY19 (2), FY20
Women's Heart Disease	FY18 (2), FY19 (3), FY20

Highlight:
Congenital Heart Disease

The Fontan procedure is a lifesaving surgical technique performed on infants born with a single functioning ventricle, which has increased survival rates to adulthood but can lead to progressive morbidities known as Fontan failure. Through support of a FY15 TTDA, Dr. William Weiss developed the Fontan Circulation Assist Device (FCAD), a small implantable blood pump to be utilized in adult patients with progressive Fontan failure. The FCAD is the first to augment right-sided circulation and was successfully tested in a large animal model over a 30-day period. Dr. Weiss received follow-on support, through a FY19 Expansion Award-Funding Level 3, to further develop the FCAD as a permanent, long-term, right heart replacement.

Endocrine/Metabolism

FY18-FY20 Awards by Primary and Secondary Topic Areas

Diabetes	FY18 (19), FY19 (28), FY20
Endometriosis	FY18 (9), FY20
Familial Hypercholesterolemia	New in FY20
Fibrous Dysplasia	New in FY20
Mitochondrial Disease	FY18 (5), FY19 (11), FY20
Nutrition Optimization	FY18 (1), FY19 (3), FY20
Pancreatitis	FY18 (6), FY19 (5), FY20

Highlight:
Endometriosis

Women living with endometriosis experience excruciating pain and possible infertility. Endometriosis, a disorder in which abnormal tissue grows outside the uterus, is dependent on angiogenesis. While FDA-approved angiogenesis inhibitors are available for other indications, the potential for teratogenic side effects makes this class of therapeutics inappropriate for use in reproductive-age women. Through a FY18 PRMRP CTA, Dr. Amy DiVasta is repurposing and testing another commercially available angiogenesis inhibitor that is comparatively safer to treat endometriosis: cabergoline, which has been shown to reduce pelvic pain and is used to treat other hormone imbalances. This Phase II clinical trial is underway.

[1] Scleroderma research is now covered under the Scleroderma Research Program (SRP), which was initiated in FY20

Environmental Health & Respiratory Health and Injury

FY18-FY20 Awards by Primary and Secondary Topic Areas

Environmental Health

Burn Pit Exposure	FY18 (2), FY19 (0), FY20
Constrictive Bronchiolitis	FY18 (2), FY19 (0), FY20
Metals Toxicology	FY18 (1), FY19 (0), FY20

Respiratory Health and Injury

Acute Lung Injury	FY18 (9), FY19 (12)
Lung Injury	FY18 (10), FY19 (14)
Pulmonary Fibrosis	FY18 (9), FY19 (16), FY20
Respiratory Health	FY18 (18), FY19 (16), FY20

Highlight:

Pulmonary Fibrosis

Current therapies are limited for the treatment of acute radiation illness as a result of exposure to high doses of ionizing radiation (i.e., nuclear attack or therapeutic radiation as a cancer treatment). BIO300 is a current countermeasure that has demonstrated efficacy against the long-term damaging effects of radiation exposure in cancer patients and is currently used by those patients in an orally-administered drug. This FY16 TTDA, led by Dr. Michael Kaytor, has resulted in the identification of a dry, solid dosage form which would facilitate the carrying of this medical countermeasure into high-risk, austere environments. This project has received additional funding for the continued development and scaling-up of a field-deployable medical product for the Warfighter. Additionally, Dr. Kaytor has overseen the development of BIO300 as a therapy for COVID-19 with a clinical trial supported by the National Institute of Allergy and Infectious Diseases, as well as an FY20 PRMRP Expansion Award that was recently recommended for funding.

"Environmental Health" and "Respiratory Health and Injury" constitute two separate and distinct PRMRP research portfolios. They are combined here due to space limitations.

Infectious Diseases

FY18-FY20 Awards by Primary and Secondary Topic Areas

Antimicrobial Resistance	FY18 (16), FY19 (21)
Emerging Infectious Diseases	FY18 (19), FY19 (21)
Emerging Viral Diseases	New in FY20
Hepatitis B	FY19(2) & FY20
Hepatitis B and C	FY18 (3)
Malaria	FY18 (6)
Pathogen-Inactivated Blood Products	FY18 (1), FY19 (2), FY20
Plant-Based Vaccines	New in FY20
Tuberculosis	FY18 (4), FY19 (6)
Vaccine Development for Infectious Disease	FY18 (26)

Highlight:

Dengue

Partnering PIs, Dr. Shirit Einav and Dr. John Dye received an FY15 Investigator-Initiated Research Award to optimize novel selective inhibitors of two major regulators of viral infection, AP2-associated protein kinase 1 (AAK1) and cyclin G-associated kinase (GAK). Detailed stability and pharmacokinetic studies have been performed on several lead compounds and results have shown broad-spectrum activity of several AAK1 and GAK inhibitors against dengue, Ebola, and chikungunya. In vivo experiments are planned, with the ultimate goal of selecting several pre-IND candidates. If successful, this may be a viable approach for treating other AAK1- and GAK-implicated diseases beyond viral infections.

Internal Medicine

FY18-FY20 Awards by Primary and Secondary Topic Areas

Focal Segmental Glomerulosclerosis	FY18 (5), FY19 (5), FY20
Interstitial Cystitis	FY18 (2), FY19 (0), FY20
Polycystic Kidney Disease	FY19 (12), FY20
Sustained-Release Drug Delivery	FY18 (4), FY20

Highlight:

Polycystic Kidney Disease

Autosomal dominant polycystic kidney disease (ADPKD) is a severe genetic disorder characterized by progressive enlargement of the kidney, eventually leading to kidney failure. Dr. Michael Chonchol received a FY16 CTA to examine the efficacy of pravastatin in decreasing kidney growth and improving kidney function in adult ADPKD patients. To date, 99 patients have completed the 6-week safety assessment and 2 have completed the end-of-study 2-year visit with no noted issues or concerns. The results from this study will provide the first insights into the efficacy of a statin for the improvement of renal function in ADPKD adult patients, which could immediately impact clinical practice.

Neurology

FY18-FY20 Awards by Primary and Secondary Topic Areas

Cerebellar Ataxia	FY18 (2), FY19 (0)
Chronic Migraine and Post-Traumatic Headache	FY18 (2), FY19 (0), FY20
Dystonia	FY18 (5), FY19 (2), FY20
Frontotemporal Degeneration	FY18 (4), FY19 (5), FY20
Hydrocephalus	FY18 (0), FY19 (3), FY20
Myotonic Dystrophy	FY18 (3), FY19 (3), FY20
Spinal Muscular Atrophy	FY18 (0), FY19 (0), FY20
Tinnitus	FY18 (2), FY19 (0), FY20

Highlight:

Chronic Migraine and Post-Traumatic Headache

The most common symptom that develops in patients following an mTBI is post-traumatic headache (PTH). While PTH resolves in a subset of patients, many experience persistent symptoms for which there are currently no approved treatments. As part of a FY18 FPA, Dr. Todd Schwedt and his colleagues are conducting a Phase II clinical trial at the Mayo Clinic that evaluates calcitonin gene-related peptide receptor monoclonal antibody as a treatment for PTH. If successful, this trial will provide evidence necessary for initiation of a Phase III treatment trial for PTH. The FPA is a collaboration between Mayo Clinic, Phoenix VA Healthcare System, Luke Air Force Base, University of Arizona, Arizona State University, and The Translational Genomics Research Institute.

Orthopedic & Regenerative Medicine

FY18-FY20 Awards by Primary and Secondary Topic Areas

Arthritis	FY18(2), FY19(3), FY20
Epidermolysis Bullosa	FY18 (1), FY19 (0), FY20
Musculoskeletal Disorders	FY18 (9), FY19 (18)
Musculoskeletal Health	New in FY20
Nanomaterials for Bone Regeneration	FY19 (4)
Post-Traumatic Osteoarthritis	FY18 (11) & FY19 (10)
Pressure Ulcers	FY18 (3), FY19 (0), FY20
Tissue Regeneration	FY18 (21), FY19 (24)

Highlight:

Post-Traumatic Osteoarthritis

Dr. Steven Ghivizzani and colleagues are optimizing for clinical use a gene therapy-based technology that drives expression of anti-arthritic proteins directly from the diseased tissue. Investigators have demonstrated in both small and large animal models that this potential therapeutic remained active for more than a year after a single dose. The therapeutic prevented development of osteoarthritis (OA) after acute injury as well as prevented disease progression and reduced symptoms in joints with established OA. Current efforts supported by a FY18 TTDA are focused on increasing targeting and durability of the therapeutic.

Psychological Health

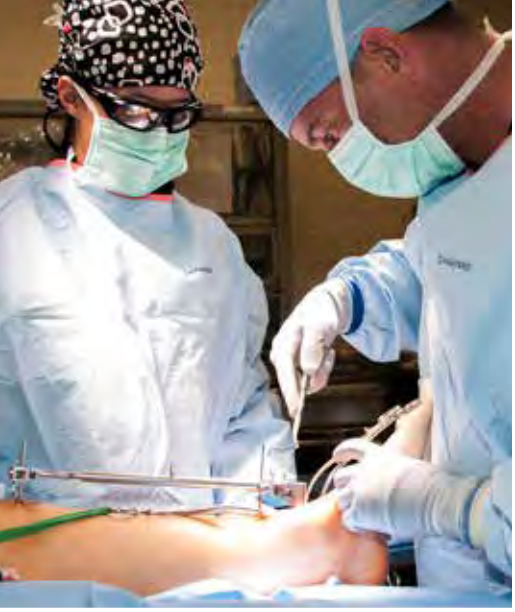
FY18-FY20 Awards by Primary and Secondary Topic Areas

Chronic Pain Management	FY18 (12)
Eating Disorders	FY18 (7), FY19 (1), FY20
Fragile X	FY18 (2), FY20
Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome	New in FY20
Non-Opioid Pain Management	FY18 (4)
Resilience Training	FY19 (1), FY20
Rett Syndrome	FY18 (2), FY19 (1)
Sleep Disorders	FY18 (3), FY19 (6)
Sleep Disorders and Restriction	New in FY20

Highlights:

Sleep Disorders

Chronic insomnia is a debilitating disease faced by many Service members and is a risk factor for depression, suicidality, substance abuse, and PTSD. Cognitive behavior therapy for insomnia (CBT-I) is the most effective treatment in the civilian population, with fewer side effects and better long-term outcomes than pharmaceuticals; however, there are not enough trained providers to meet the current military demand. With a FY16 TTDA, Dr. Daniel Taylor and his team have developed a web-based CBT-I course (CBT-IWeb) as a fully sustainable, accessible, and cost-effective means of training for providers. A pilot study is underway comparing the efficacy of CBT-IWeb to standard, in-person CBT-I training and to date, 817 providers have completed training.



PEER REVIEWED ORTHOPAEDIC RESEARCH PROGRAM

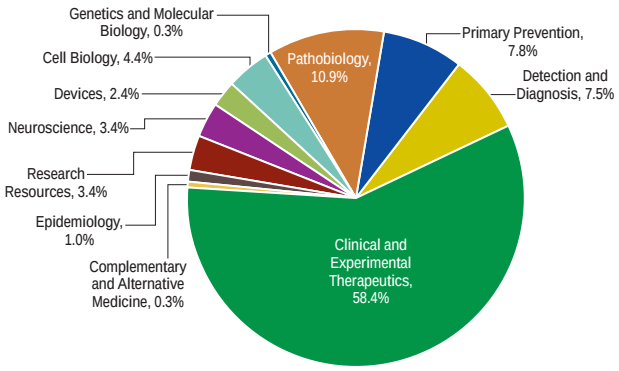
Program History

Since its inception in 2009, the DOD Peer Reviewed Orthopaedic Research Program (PRORP) has dedicated its congressional appropriations, totaling $428.5M through FY20, to supporting military-relevant orthopaedic research that will also benefit the treatment and care of orthopaedically injured persons in the general population. To date, the PRORP has funded 274 projects (with an additional 21 awards planned by September 30, 2020) that have focused research on orthopaedic topics, including treatment, rehabilitation, prevention of complications, and prosthetics/orthotics.

Relevance to Military Health

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

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



FY09-FY19 PRORP Portfolio Investment by SCS Code

Vision: **Provide all Warriors affected by orthopaedic injuries sustained in the defense of our Constitution the opportunity for optimal recovery and restoration of function**

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

"The PRORP really tries to focus on research that's going to benefit those directly involved and who have been injured in combat situations, and unique combat situations that maybe we don't see in everyday medical practices—things such as horrific multi-limb injuries, penetrating pelvic injuries, a huge amount of loss of muscle or function to a limb. So the program is really trying to focus on research to bridge those gaps that we have no answers to right now."
CAPT Eric Hofmeister, M.D. (USN, Ret.), PRORP Programmatic Panel

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

[2] Hauret KG, Jones BH, Bullock SH, et al. 2010. Musculoskeletal injuries: Description of an under-recognized injury problem among military personnel. *American Journal of Preventative Medicine* 38(1S) S61-S70.

[3] Teyhen DS, Goffar SL, Shaffer SW, et al. 2018. Incidence of musculoskeletal injury in US army unit types: A prospective cohort study. *Journal of Orthopaedic and Sports Physical Therapy*. 48(10) 749-756.

[4] Corss JD, Ficke JR, Hsu JR, et al. 2011. Battlefield orthopaedic injuries cause the majority of long-term disabilities. *The Journal of the American Academy of Orthopaedic Surgeons* 19 Suppl 1 S1-S7.

Focus Areas

The orthopaedic care field has benefited from many successes; however, many challenges still exist that prevent some injured patients from returning to their pre-injury level of fitness. The research field's ability to address these challenges has a direct impact on the readiness of the US military, the rehabilitation and reintegration of our Veterans, and the clinical care of patients in the general public. To meet this need, the FY20 PRORP requires all applications to address at least one of the following PRORP Focus Areas:

- Limb Stabilization and Protection
- Retention strategies for use at the point of injury or to facilitate return to duty
- Translation of early findings in soft tissue trauma or fracture-related infection
- Tissue Regeneration Therapeutics
- Compartment Syndrome
- Osseointegration
- Orthotic Devices

Recent Advances in Orthopaedic Research

New Information in Our Understanding of Osteoarthritis Onset

Tamara Alliston, Ph.D., University of California, San Francisco
Alexis Dang, M.D., and Alfred Kuo, Ph.D., San Francisco Veterans Affairs Medical Center

With a FY13 Idea Development Award, Dr. Tamara Alliston and her team investigated the role of subchondral bone and osteocyte-mediated perilacunar/canalicular remodeling (PLR) in the development of OA. Dr. Alliston and her team analyzed the OA tissue in comparison to tissue without OA and established that patients with late-stage OA have demonstrable changes to their subchondral bone, including reduced lacunocanalicular network (LCN) size, increased mineralization, and misaligned bone matrix fibers. The team also demonstrated that MMP13 production by osteocytes positively correlates with LCN area and length, suggesting that suppression of PLR also correlates with human OA. To determine whether osteocytes and deregulated PLR are at the root of OA induction, Dr. Alliston's group specifically deleted the MMP13 gene from otherwise normal osteocytes in a mouse model. The absence of MMP13 mimics deregulated PLR and OA-associated phenotypes in subchondral bone, including increased mineralization, significant reduction of the LCN, and modest alteration of matrix fiber alignment. Importantly, this deregulation of PLR led to an increase in OA-like articular cartilage degradation, suggesting that disruption of normal osteocyte function may induce the onset of OA. The result of Dr. Alliston's work, published in 2019 in the journal *Bone Research*, advances the understanding of significant gaps in the knowledge of OA mechanisms associated with development of joint disease.

Seeking Multimodal Vaccines to Eradicate Biofilm-Associated Microorganisms Following Traumatic Musculoskeletal Injury

Mark Shirtliff, Ph.D., and Janette Harro, Ph.D., University of Maryland, Baltimore

With a FY14 Idea Development Award, Dr. Mark Shirtliff and Dr. Janette Harro set out to investigate biofilm-specific vulnerabilities in order to develop a vaccine to eliminate the incidence and persistence of these infections. The Shirtliff/Harro team created a novel pentavalent vaccine, which combined their previous vaccine with an additional immunizing agent that specifically targets the planktonic form of *Staphylococcus aureus (S. aureus)*. Administration of the new pentavalent vaccine initially provided mice with a significant reduction in mortality relative to controls when challenged with an *S. aureus* infection, and 66.7% of these surviving mice demonstrated no evidence of infection at the injection site. The pentavalent vaccine also provided dramatic improvement in survival when compared to either the quadrivalent or planktonic protein alone after a very high dose of *S. aureus*. Finally, the research determined that these improvements in the context of infection were a definitive result of the immune response generated by vaccination, as simply dosing mice with the antibodies generated against these five *S. aureus* proteins significantly enhanced overall survival and bacterial clearance relative to controls. The important advances generated by the team of Drs. Shirtliff and Harro, published in 2019 in the journal *Infection and Immunity* suggests the need to translate their vaccine into human trials to expedite the potential benefits to wounded warriors.

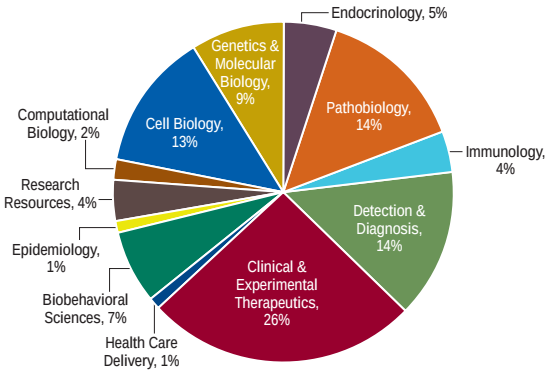
PROSTATE CANCER RESEARCH PROGRAM

Vision: **Conquer prostate cancer**

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

Program History

Since its inception in 1997 and over its 23-year history of congressional support totaling nearly $1.93B, the Peer Reviewed Prostate Cancer Research Program (PCRP) has changed the landscape of biomedical research and energized the prostate cancer 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 prostate cancer; has been the leading supporter of research aimed at understanding and resolving disparities in prostate cancer incidence and mortality; and has fostered the development of over a thousand young investigators, many of whom have become leaders in cutting-edge research that is making a significant difference for millions of patients with prostate cancer.



FY17-FY19 PCRP Portfolio Investment by SCS Code

Overarching Strategic Goals

In 2018, the PCRP developed a Strategic Plan that outlines the program's 5-year strategy for funding innovative and impactful ideas that will ultimately lead to the elimination of death from prostate cancer. For 2020, the program continues its work on addressing the four overarching strategic goals that focus on addressing lethal prostate cancer, health disparities, and improving quality of life for survivors, all of which are designed to provide further advancements that will impact current and future prostate cancer patients:

- Improve the quality of life for survivors of prostate cancer
- Develop treatments that improve outcomes for men with lethal prostate cancer
- Reduce lethal prostate cancer in people of African descent, Veterans, and high-risk or underserved populations
- Define the biology of lethal prostate cancer to reduce death

"For more than 20 years, the program has leveraged cutting edge prostate cancer biology and innovative clinical trials to reduce the lethality of prostate cancer. Success measured through innovative new drug therapies and better understanding of the underlying mechanisms of prostate cancer risk and response is uniquely focused and delivered to patients and their families through the PCRP."

David Quinn, M.B.B.S., Ph.D., F.R.A.C.P., F.A.C.P., FY20 PCRP Programmatic Panel Chair, University of Southern California

Impacting Patients in the Military Health System

PCRP-investments have led to FDA-approval of treatments that are now standard of care and are broadly impacting prostate cancer patients, including those treated in the Military Health System. Thousands of patients in the Military Health System, including active duty Service members and Veteran retirees, have benefited from treatment with these drugs with more than 103,224 prescriptions written since these agents were FDA-approved.

These prescription and patient numbers are within the Military Health System only and not the general public.

Drug	Prescriptions	Patients	Approval Year
XGEVA® (Denosumab)	7,094	740	2010
Zytiga® (Abiraterone acetate)	54,244	5,478	2011
Xtandi® (Enzalutamide)	41,099	4,436	2012
Erleada® (Apalutamide)	787	176	2018

Patient and prescription data provided by the DHA Pharmacy Analytics Support Section (PASS) based on records maintained in the Pharmacy Data Transaction Service (PDTS) Data Warehouse.

Increasing Diversity in Prostate Cancer Clinical Trials

To address the healthcare needs of populations disproportionately affected with prostate cancer, the PCRP's Prostate Cancer Clinical Trials Consortium (PCCTC) has strived to increase diversity in prostate cancer clinical trials. Across the 10 PCCTC clinical sites, an average of 13% of enrolled patients are from minority and underserved populations, with some centers achieving 30%-40% of their accrual from diverse populations due to specific outreach efforts to local healthcare systems for African Americans and rural counties. The PCCTC is also leading the global International Registry to Improve Outcomes in Men with Advanced Prostate Cancer (IRONMAN) patient registry effort to gather patient information from a diverse group of 5,000 men with advanced prostate cancer. These collective contributions of the PCCTC will provide outcomes data that will hopefully shed light on the underlying factors contributing to prostate cancer health disparities.

PCRP Research Advancements

Jennifer Wu, Ph.D., Northwestern University

With the support of an FY05 Idea Development Award, Dr. Jennifer Wu made the discovery that cancer cells in advanced stages of prostate cancer are able to survive by escaping immune system surveillance and disabling immune responses. The mechanisms for these events involve the oncogenic stress-induced molecule called "MIC." During cancer development, prostate cells express MIC on their surface, "flagging down" immune cells and initiating their response in fighting cancer cells. This process is eliminated in advanced prostate cancer, allowing cancer cells to bypass immune surveillance and roam free. More detrimentally, cancer cells release a soluble form of MIC, called sMIC, which shuts down the immune system and allows cancer cells to "dodge" immune cells. Dr. Wu developed a first-in-class monoclonal antibody to target sMIC, and she and her colleagues are working toward bringing this anti-sMIC antibody to the clinic by conducting preclinical safety assessment for clinical trials, examining the antibody's role in current standards of care for prostate cancer, and investigating use of the antibody to tackle neuroendocrine prostate cancer, the most lethal type. With support from an FY14 Idea Development Award, Dr. Wu has more accurately studied the interaction between prostate cancer cells and the immune system and, through collaboration with the pharmaceutical industry, hopes to further validate the efficacy of her antibody as a therapy and enable its use in patients in the near future.

Samuel Denmeade, M.D., Johns Hopkins University

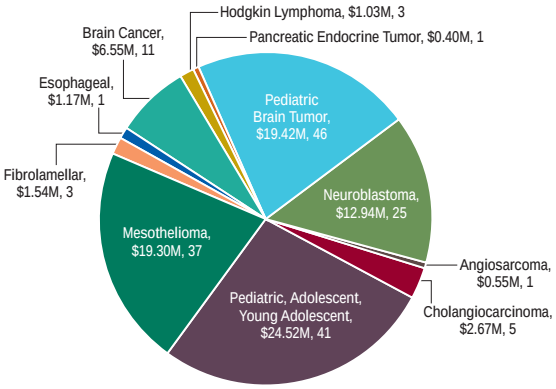
Treatments to block or lower testosterone have been standard for prostate cancer since the 1940s; however, recent observations suggest re-exposure to testosterone following chronic androgen deprivation in castration-resistant prostate cancer (CRPC) cell lines causes apoptosis (cell death). Bipolar androgen therapy (BAT) builds on this novel finding by rapidly cycling between supra-physiological (high) and castrate (low) concentrations of testosterone, resulting in DNA disruption/damage and cancer cell apoptosis. With support from an FY13 Transformative Impact Award, a Johns Hopkins University (JHU) team led by Dr. Samuel Denmeade performed a clinical study to evaluate the efficacy of BAT in men with metastatic castration resistant prostate cancer. Men whose prostate cancer had developed hormone therapy resistance began responding to hormone therapy again after BAT, and some experienced the positive side effects of enhanced quality of life and restored sexual function. Dr. Denmeade's team then completed a randomized Phase II study evaluating BAT in men with metastatic CRPC progression following enzalutamide treatment. Fifty-two percent of men treated with BAT followed by enzalutamide achieved a 50% decline in prostate-specific antigen concentration compared to 30% of those treated with BAT alone. In FY19, the JHU team received a Clinical Trial Award to further evaluate the efficacy of BAT using repeat cycling of BAT and enzalutamide.

"Serving as a consumer reviewer on the scientific review panels is absolutely fulfilling! The PCRP allows me to continue my personal and professional growth with prostate cancer which provides a viable and reliable voice for our non-profit organization—the Georgia Prostate Cancer Coalition (GPCC). The more immersed I am in the prostate research, the more GPCCs advocacy can serve the community here in Georgia. Most importantly, the PCRP has made a significant impact not only for me, but also for the broader prostate cancer community. I hope that the PCRP continues to be funded until PC no longer exists for men! HooaH!"
LTC Clarence Luckett, PCRP Consumer Peer Reviewer, Georgia Prostate Cancer Coalition Board Member

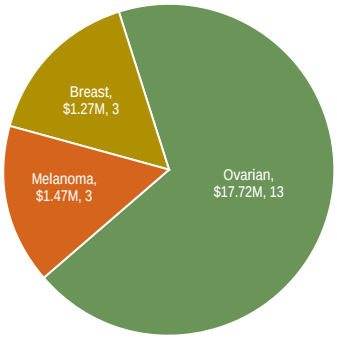
RARE CANCERS RESEARCH PROGRAM

Rare Cancers and Peer Reviewed Rare Cancer Research Program (RCRP) History

Major obstructions in patient care of rare cancers are lack of information, therapeutics, and in-depth research, specifically, lack of available patient tissues, cell and tumor models for research; lack of understanding of the tumor biology and cell of origin of rare cancers; lack of infrastructure for sharing data and other resources; and lack of collaboration among researchers, clinicians, patients/advocacy groups to advance rare cancers research needs. Rare cancer patients are almost seven times less likely to have an approved targeted therapy compared to patients with other cancers. As of November 2018, over 100 rare cancers had no publicly available datasets on the Gene Expression Omnibus repository, a major source of publicly available data.[1] The CDMRP has seven cancer-specific programs. The rare cancers research topic area was first introduced under the Peer Reviewed Cancer Research Program (PRCRP) in FY19, although the PRCRP has funded research on rare cancer types/subtypes before 2019. To date, the PRCRP has funded several rare cancer types/subtypes,[2] totaling over $90M (top figure). Various rare cancers topic/sub-topic areas have been awarded by the Breast Cancer Research Program (FY92-FY19), Melanoma Research Program (FY19), and the Ovarian Cancer Program (FY99-FY19) (bottom figure), totaling over $20.47M.



Rare Cancer Types/Subtypes funded by the FY09-FY19 PRCRP (Graph depicts the total dollar amount and number of awards funded)



Rare Cancer Research Funding from other CDMRP Cancer Programs except PRCRP

In FY20, Congress directed $7.5M specifically to rare cancers research in the DOD appropriation, thus establishing the RCRP. The RCRP defines rare cancer as cancers affecting less than 6 persons per 100,000 per year in the US. With roughly 200 cancers meeting the RCRP's definition, around half a million Americans each year are impacted by rare cancers.[3] FY20 Program Announcements to be solicited for are the Concept Award, Idea Development Award and Resource and Community Development Award. This new program will continue investment in research focusing on advancing the understanding of rare cancers for the benefit of Service members, Veterans, their families, and the American public.

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

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

"I am the Associate Director of "Count Me In;" the co-founder of Angiosarcoma Awareness, Inc., and a research scientist at the Broad Institute of MIT and Harvard. In 2010, I was diagnosed with angiosarcoma. I have combined my cancer advocacy and scientific background to engage with patients in order to build and carry out patient-partnered genomics studies. Serving on the RCRP Program Programmatic Panel will allow me to utilize my expertise to advance the goals of the RCRP."
Corrie Painter, Ph.D., Broad Institute of MIT, and Count Me In; Consumer and Scientist, FY20 RCRP Programmatic Panel member

[1] Rare Cancer's "Valley of Death." American Association of Cancer Researchers, Abstract 2505, Atlanta, 2019.
[2] Rare cancer types/sub types with <6 incidence rate per 100K, and are representative of FY20 PRCRP topics.
[3] DeSantis, CE. 2017. The burden of rare cancers in the United States. *CA Cancer J Clin* 67:261-272.

FY20 RCRP Award Mechanism Key Elements and Funding Information:

Award Mechanism	Key Elements	Funding
Concept Award (CA)	Supports development of highly innovative, untested, and potentially groundbreaking concepts in rare cancer field	Maximum funding of $100k for direct costs (plus indirect costs) for up to 1 year
Idea Development Award (IDA)	Supports innovative and high-risk/high-reward research with the potential to yield impactful data in the rare cancer field	Maximum funding of $350k for direct costs (plus indirect costs) for up to 3 years
Resource and Community Development Award (RCDA)	Supports research resources development to facilitate collaboration and information sharing among stakeholders such as researchers, patients, caregivers, clinicians, and other members of the rare cancers community	Maximum funding of $600k for direct costs (plus indirect costs) for up to 3 years

Focus Areas

During the FY20 Vision Setting meeting, the programmatic panel decided on the following lists of Focus Areas that applicants need to address:

FY20 RCRP Focus Areas:

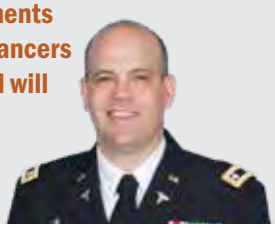
Focus Areas	Award Mechanisms that Apply
Biology and Etiology: Identify disease-defining molecular pathways, cell context, and microenvironment.	CA and IDA
Research Model: Develop and validate rare tumor-specific models that can support clinical trial readiness.	CA and IDA
Platform Development: Development of platforms (such as, tumor tissue repository with clinical annotation; centralized databanks; patient registry with common data structure; research model and Omics database; longitudinal studies of natural history and treatment response) for multiple rare cancers, to allow sharing of data, bio-specimens, and resources.	CA and RCDA
Therapy: Identify novel therapeutic strategies, including drug repurposing.	CA and IDA

"As an oncologist and scientist with a longstanding interest in rare tumor syndromes, it is an honor and a privilege for me to serve as Chair of the RCRP Programmatic Panel. This Program provides a unique opportunity to make critical advances toward effective therapy for rare tumors. For many rare tumors, there is a near-complete lack of understanding of their cause, and some have never benefitted from research of any kind. We expect this program to catalyze pivotal discoveries that lead directly to the first-ever effective therapeutic strategies for rare tumors. We further expect broad benefits to the cancer research community, with impact on other more common tumor types, since rare tumors often provide critical insight into the cause of more common tumors."

Elizabeth P. Henske, Brigham and Women's Hospital, Boston, MA, FY20 RCRP Programmatic Panel Chair

"The idea to start the RCRP seems obvious, especially within the CDMRP, which already has mechanisms that fund rare cancers and diseases such as neurofibromatosis, tuberous sclerosis, and specific cancers such as pediatric brain tumors in the PRCP. But this new mechanism takes the commitment to funding rare cancers one step further. The RCRP offers investigators multiple different avenues to submit proposals without requirements for preliminary data and with those funding mechanisms being created specifically with rare cancers in mind. I am confident that this program will lead to novel research studies and programs and will shine an even brighter light on rare cancer research."

LTC Brett J. Theeler, M.D., Walter Reed National Military Medical Center, Bethesda, MD, FY20 RCRP Programmatic Panel member



RECONSTRUCTIVE TRANSPLANT RESEARCH PROGRAM

Program History

The Peer Reviewed Reconstructive Transplant Research Program (RTRP) was initiated in 2012 to provide support for research of exceptional scientific merit that has the potential to make a significant impact on improving the function, wellness, and overall quality of life for injured military Service members and Veterans, their caregivers and family members, and the American public. Appropriations for the RTRP from FY12 through FY19 totaled $93M. The FY20 appropriation is $12M.

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

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

Mission: **Expand reconstructive options for catastrophically injured Service members, Veterans, and American civilians by developing a standardized conduct of VCA procedures**

"The CDMRP RTRP has been instrumental in moving the field of VCA forward, ensuring sound research. The long term, strategic program goals of increased access to VCA and reduced morbidity from immunosuppression will ensure the procedure is available to those catastrophically wounded service members for whom there are no other options to restore form, function and appearance."
Wendy Dean, M.D., MI-Healthcare Consultants, LLC, RTRP Programmatic Panel Member

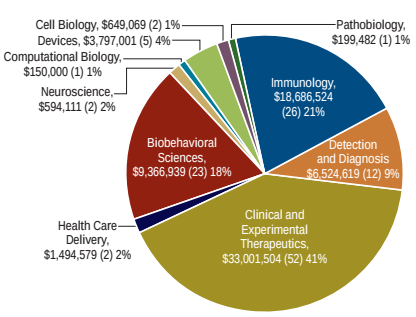
FY20 Focus Areas

Investigator-Initiated Research Award

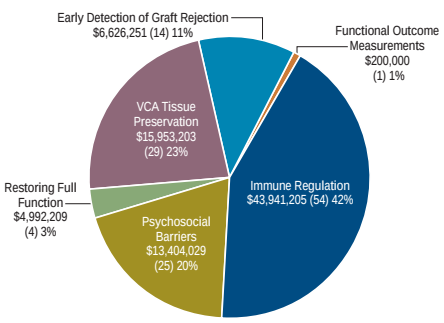
- Reduce the risks of VCA-associated immunosuppression
  - Define the unique mechanisms of VCA immunogenicity
  - Develop novel approaches for improving VCA immune tolerance
  - Identify unique immunosuppression requirements for VCA compared to other solid organ transplants
- Develop reliable non-invasive methods or tools for monitoring VCA graft rejection
  - Develop reliable non-invasive biomarkers for monitoring chronic VCA graft rejection in a large animal model
  - Identify and/or validate new peripheral biomarkers for acute and chronic rejection
  - Develop assays or devices for clinical graft monitoring utilizing validated biomarkers
- Advance existing or develop innovative ex vivo tissue preservation strategies to extend the timeline between procurement and transplantation
  - Develop novel approaches and models for perfused, hypothermic, high subzero and low subzero, or static preservation strategies
  - Determine the extent to which VCA tissue preservation technology impacts VCA immunogenicity

Clinical Network Development Award

- Patient inclusion/exclusion criteria
- Patient education
- Surgical procedures
- Immunosuppression and/or immunoregulation
- Outcome metrics
- Quality of life measures
- Rehabilitation
- Patient reporting (e.g., registry)



FY12-FY19 RTRP Portfolio Investment by SCS Code (Number of Awards)



FY12-FY19 RTRP Portfolio Investments by Barrier (Number of Awards)

Consumer Story

Rick Cicero: Double Amputee Doubling Down for Scientific Advances

Rick Cicero has a long history of serving the military in various capacities, including as an Army Special Operation Force Paratrooper, a National Guardsman, and finally as a civilian contractor working with a K9 unit for the detection of explosive devices. It was in August 2010, while on foot patrol in Afghanistan, that Rick's dog detected an improvised explosive device (IED). The IED detonated as Rick approached the location, which led to significant damage to his right arm and the loss of right leg above his knee. During the course of his treatment, his badly damaged right arm developed gangrene, requiring an above-elbow amputation. He was released from the hospital in December 2010 with the aid of a cane and prosthetics on his right leg and arm. Seeking further treatment, Rick received targeted muscle reinnervation to enable improved and more intuitive control of his prosthetics. He then became the first person to undergo osseointegration at Walter Reed National Military Medical Center in 2016, first for his arm and then later for his leg. Rick served as a consumer reviewer for the first time in 2015, and enjoys working with the RTRP to have an understanding of new developments that are on the horizon for amputees who may be considering transplantation. Rick has witnessed some of the amazing results of those who have pursued that treatment option and he stresses the importance of dedicating oneself to recovery in order to get the best possible outcome.

Funded Research Highlights

Leonardo Riella, M.D., Ph.D. (left), Thet Su Win, M.D., Ph.D. (center), and Bohdan Pomahac, M.D.

Biomarkers to Predict Rejection in Vascularized Composite Allotransplantation

Leonardo Riella, M.D., Ph.D. and Bohdan Pomahac, M.D., Brigham and Women's Hospital, Inc.

VCA recipients must adhere to lifelong immunosuppression regimens, yet more than 80% of recipients will experience an episode of acute rejection within the first year. Novel non-invasive biomarkers for the diagnosis of VCA graft rejection are needed as an alternative to the current reliance on skin biopsies and the Banff classification system to better manage VCA patient care and predict and monitor rejection episodes. Drs. Leonardo Riella and Bohdan Pomahac at Brigham and Women's Hospital have analyzed serum samples from six face transplant recipients collected over a follow-up range of 12-54 months, representing episodes of no-rejection, non-severe rejection, and severe rejection. Using a novel proteomic platform, a signature of five proteins capable of discriminating severe rejection from no-rejection and non-severe rejection was identified. Of these, MMP3 (Matrix Metalloproteinase 3) showed the highest levels of upregulation and was further validated using enzyme-linked immunosorbent assay, a standard immunoassay technology. Although additional validation is needed, this may lead to better understanding of the molecular process underlying rejection as well as better methods of detecting and preventing rejection.

Increasing Organ Donor Authorization for Vascularized Composite Allotransplantation

Heather Gardiner, Ph.D., MPH; Laura Siminoff, Ph.D., Temple University

Organ Procurement Organization (OPO) request staff are responsible for approaching families of deceased organ donors to obtain donation authorization for both solid organs and grafts for VCA. The limited awareness of the need for and benefits of VCA among both OPO request staff and the general public makes securing family authorization for these donations challenging. Drs. Heather Gardiner and Laura Siminoff at Temple University are addressing this challenge. Telephone surveys were conducted with 157 OPO requesters nationwide, and results indicated that nearly 65% of OPO requesters lack VCA-specific training, while 70% lack experience in requesting for VCA donation. When asked to assess their own knowledge of VCA on a ten-point scale (1 = not knowledgeable at all and 10 = very knowledgeable) OPO requesters had a mean score of 2.8. Focus groups with the general public (N=54) and donor families (N=11) revealed a greater hesitancy to consider VCA compared to solid organ donation. In the next phase of their study, the team will adapt the Communicated Effectively about Donation (CEaD) training program currently used by OPO request staff, for VCA donation.

"The DOD has been the primary supporter of the effort to make hand and face transplants a reality for both the Warfighter and civilians. We envision a day when the research we support will overcome the significant hurdles to this clinical option and anyone who needs a new face or hand can get one."
Lloyd Rose, Ph.D., Department of the Army, Civilian, RTRP Programmatic Panel Member

SCLERODERMA RESEARCH PROGRAM

Program History

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

To address the significant research gaps in scleroderma, Congress directed that the Peer Reviewed Scleroderma Research Program (SRP) be included in the US FY20 DOD appropriations at $5M. Prior to this appropriation, scleroderma was a PRMRP topic area in FY08, FY10-FY13, and FY15-FY19. From FY08 through FY19, the CDMRP has overseen a topic-specific investment of over $23M in scleroderma research.

A request for information (RFI) was released and an inaugural Stakeholders meeting was held to identify barriers in scleroderma research, address key knowledge and scientific gaps, and identify approaches for the treatment of scleroderma. The RFI asked survey respondents to address the most critical needs in scleroderma research. The results of the RFI, complied from over 60 responses, were used to inform stakeholders of funding gaps, challenges facing the scleroderma community, and potential research priorities. The SRP held a Stakeholders meeting bringing together representatives from scleroderma non-profit organizations, academia, and government institutions. This diverse group of 40 individuals shared perspectives on which initiatives have the greatest potential to propel the science forward, break down barriers in research and patient outcomes, address key knowledge or scientific gaps, and identify approaches for the treatment of scleroderma. Following the Stakeholders meeting, a Programmatic Panel comprised of clinicians, research scientists, and consumer advocates met at Vision Setting and used the information gathered from the Stakeholders meeting to develop the Vision, Mission, and current and long-term strategic goals for the program. Panel members also used research priorities identified during the Stakeholders meeting to craft Focus Areas, which will be used in Program Announcements to solicit scleroderma research of the highest impact, innovation, and translation.

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 improved therapies, and ultimately, a cure for scleroderma for Service members, Veterans and the American public**

"The focus of this grant program is on research that will benefit patients with scleroderma. It is important that we acknowledge that current standard treatment approaches do not fundamentally alter the overall course of this disease. A 2012 paper published in the journal *Rheumatology* indicated that there had been no improvements in standardized mortality rates for patients diagnosed with systemic sclerosis in the preceding 40 years.
In considering research grant applications, we need to be open to new treatment approaches that may be "outside the box," as long as they have a reasonable safety profile and sound science behind them."
Ed Harris, Founder Scleroderma Education Project, SRP Stakeholder and Consumer

FY20 Focus Areas

Idea Development Award & Idea Development Award-New Investigator Collaboration Option

- Development of clinical trial platforms that enable the rapid comparison of different therapeutic approaches on pilot basis
- Define biomarkers ('omics and/or molecular markers, cell subsets, imagining, patient-reported outcomes) that help inform therapeutic choices (immunosuppressive/anti-fibrotic) or predict course (morbidity) and quality of life
- Secondary analysis of scleroderma, and other similar disease datasets, to identify novel targets and biomarkers that can be validated in existing or new models

Translational Research Partnership Award

- Understanding the different biological/metabolic pathways that differentiate subsets of patients (gender, age, genetic, clinical phenotype, race/ethnicity)
- Utilizing systems biology and multi-omics appraches to understand the heterogeneity of disease, prevention, therapeutics inventions, and screening
- Development of cohorts from diverse populations (longitudinal) to validate potential biomarkers (i.e., replication studies)
- Define biomarkers ('omics and/or molecular markers, cell subsets, imagining, patient-reported outcomes) that help inform therapeutic choices (immunosuppressive/anti-fibrotic) or predict course (morbidity) and quality of life
- Defining epigenetic changes, multiple cell types and molecules that mediate pathogenesis

FY20 Award Mechanism

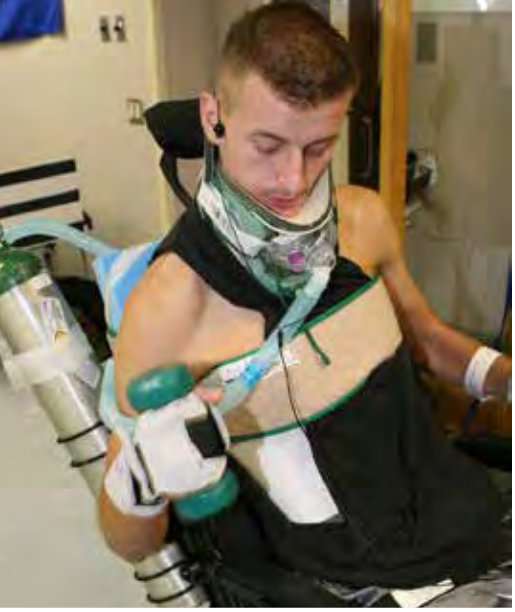
Idea Development Award/Idea Development Award-New Investigator Collaboration Option

The FY20 SRP Idea Development Award intends to support ideas that have the potential to yield high-impact findings and new avenues of investigation. This award mechanism supports conceptually innovative research that could ultimately lead to critical discoveries in scleroderma research and/or improvements in patient care. The Idea Development Award offers a New-Investigator Collaboration Option in which an established scleroderma researcher partners with an investigator in the early stages of their career to support the continued development of promising independent scleroderma investigators.

Translational Research Partnership Award

The FY20 SRP Translational Research Partnership Award intends to support partnerships between clinicians and research scientists that will accelerate the movement of promising ideas in scleroderma into clinical application. This award supports the development of translational research collaboration between two or more investigators to address a central problem or question in scleroderma in a manner that would be less readily achievable through separate efforts.

"It is both a pleasure and an honor to be part of the planning and Vision Setting for the Scleroderma Research Program. This is a great opportunity to support basic, translational, and clinical studies that will have a meaningful and lasting impact for our patients."
Maureen Mayes, M.D., University of Texas Health Science Center at Houston, SRP Programmatic Panel Chair



SPINAL CORD INJURY RESEARCH PROGRAM

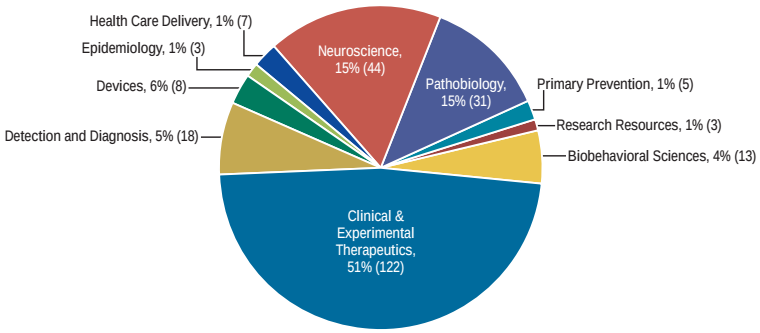
Program History

Spinal cord injuries (SCIs) are complex neurotraumatic wounds with long-term consequences requiring lifelong care. It is estimated that about 300,000 individuals are living with an SCI,[1] and this number continues to grow, as over 17,000 new cases occur in the US each year. Between 2000 and 2009, during the height of the conflicts in Iraq and Afghanistan, the rate of SCI in the military was nearly eight times that of the civilian population.[2] As a result, the VA is the largest single SCI care network, providing services for 10%–20% of all individuals living with an SCI in the US.[3]

The Peer Reviewed Spinal Cord Injury Research Program (SCIRP) was established by Congress in FY09 to support research into repairing/regenerating damaged spinal cords and improving rehabilitation therapies. With $277.85M in congressional appropriations between FY09 and FY19 for peer-reviewed spinal cord research, the SCIRP is now a leading funder of SCI research in the United States. The SCIRP supports the translation of therapeutic strategies across the continuum of care from management of the acute injury through functional and psychological rehabilitation for chronically injured individuals.

Program Portfolio

The SCIRP has funded 255 awards through FY19 across basic research, pathology detection, and diagnosis of SCI, with the largest investment in clinical and experimental therapeutics—reflecting the program's emphasis on translational and clinical research.



FY09-FY19 SCIRP Portfolio Investment by SCS Code (Number of Awards)

Current Program Priorities

The program revisits the focus and priorities annually. Considering the current research and funding landscape, the program has identified the following five Focus Areas that are aligned with and address key gaps across the continuum of care.

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

[1] https://www.nscisc.uab.edu/
[2] https://www.nature.com/articles/sc201118.pdf
[3] https://www.va.gov/opa/

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**

"I believe that the true value of the consumer is very practical – it's to give life and realism to the science, to keep everyone's eyes on the prize, the ultimate goal, the relief of real suffering of real people who need the research. I am inspired by all of the work happening in laboratories all over the country, by the passion and knowledge of the other members of my panels, and by the lived experiences of my comrade consumer reviewers."
Laurie Rappl, FY18-FY19 SCIRP Consumer Reviewer

SCI Lived Experience Consultation

The SCIRP believes that capturing and integrating the unique perspectives of people living with SCI will enable better and more impactful research outcomes. Thus, starting in FY19, SCIRP began requiring the involvement of SCI Lived Experience Consultants throughout the planning and implementation of translational and clinical research projects.

"My involvement…has been an enlightening experience which helped me to realize that there are really people and programs existing that are actively awaiting real-life input regarding mental and physical disabilities so that advancements can be made to better the quality of life of individuals facing those issues."
Sean Ferry - SCIRP Peer Reviewer, Research Participant and FY19 Award Consumer Advocate

Bridging Research and Development Toward Clinical Application

In FY16-FY17, SCIRP employed a unique funding mechanism, the Clinical Research Development Award (CRDA), with the intention to provide a small amount of capital to fund projects on the precipice of clinical application. Each project had a budget of $100,000 to get them to the next stage of development and prepare them for a future clinical study. The examples below illustrate how small, strategic investment can make a large impact on the future of SCI treatment and care.

Manual Wheelchair Virtual Seating Coach

Rory Cooper, Ph.D., University of Pittsburgh

Pressure injuries are tremendous problems for individuals with mobility and sensation impairments, harming independence and quality of life. Pressure sores can be life-threatening, as infections can develop and spread throughout the body. Dr. Rory Cooper from the University of Pittsburgh developed a Manual Wheelchair Virtual Coach (MW-VC) to reduce the incidence of pressure injuries in manual wheelchair users with a FY16 CRDA. The MW-VC system integrates sensors, artificial intelligence, and a smartphone application to track wheelchair users' seated positions and coach users to perform pressure-relieving movements to help prevent harmful pressure injuries. Dr. Cooper and his team are now ready to initiate a clinical trial with their prototype and are hopeful that this tool will improve "active seating" compliance to help prevent pressure injuries, reduce pain, and improve quality of life for people living with SCI.

Immersive Virtual Walking as Treatment for Neuropathic Pain in Spinal Cord Injury: Examining Treatment Efficacy and Cortical Mechanisms

Zina Trost, Ph.D., University of Alabama at Birmingham

Dr. Zina Trost, at Virginia Commonwealth University, laid the groundwork for a clinical trial to evaluate a virtual reality walking intervention (VRWalk) to alleviate neuropathic pain for people living with spinal cord injury. This treatment employs an immersive virtual environment where participants control an avatar that walks through virtual worlds. This intervention builds on "mirror" therapies used to alleviate phantom limb pain for amputees. Dr. Trost's FY17 CRDA provided resources and time to develop the VRWalk intervention protocol and standard operating procedures for a multi-site, randomized clinical trial that has now secured funding from a subsequent FY19 SCIRP Clinical Trial Award. Evidence points to VRWalk as a viable option for non-pharmacological treatment for SCI neuropathic pain.

Digital Avatars for Psychosocial and Integrative Health Support of Veterans with Spinal Cord Injury and Disorders

Victor Wang, CEO, MS, care.coach corporation

Poor patient compliance is a major health-related issue leading to poorer health outcomes. Mr. Victor Wang and his team at care.coach corporation have developed a virtual companion application aimed at facilitating patient engagement and making it easier for users to manage, monitor, and track their own health. With a FY17 CRDA, the care.coach digital companion or "avatar," now has the ability to converse with users while incorporating VA-developed Disease Management Protocols (DMPs) to address the unique needs of patients living with SCI. The team at care.coach believe that by allowing the digital companion to integrate the DMP questions and activities into everyday conversation and record user responses, they can overcome the major barriers to long-term DMP compliance. This idea is so compelling that three VA medical centers have now teamed up with care.coach to pilot this avatar-enabled health and wellness intervention. The VA-funded pilot study is the next step in preparing for a future multi-site clinical trial to examine the utility of this intervention to improve quality of life and other health outcomes for Veterans living with SCI.

TICK-BORNE DISEASE RESEARCH PROGRAM

Program History

The Tick-Borne Disease Research Program (TBDRP) was established in FY16, when the efforts of Lyme disease advocates led to the Peer-Reviewed Tickborne Disease Research congressional appropriation. The TBDRP has received funding at a rate of $5M annually, totaling $20M for the period FY16-FY19. In FY20, the TBDRP appropriation was increased to $7M. Each year, with input from the peer and programmatic review panels, the TBDRP strives to maximize its investment by supporting research that is innovative and impactful and aims to address fundamental knowledge gaps in the field of tick-borne diseases (TBDs).

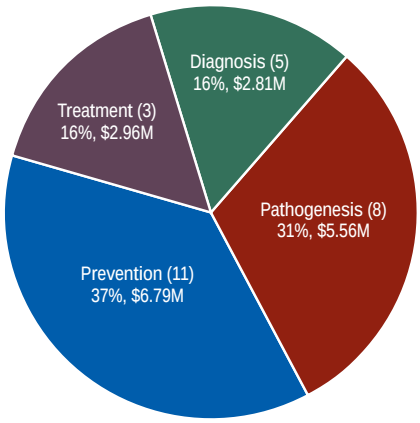
Vision: **To prevent the occurrence, better diagnose, and resolve or minimize the impact of Lyme disease and other tick-borne illnesses, with emphasis on burden of disease**

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

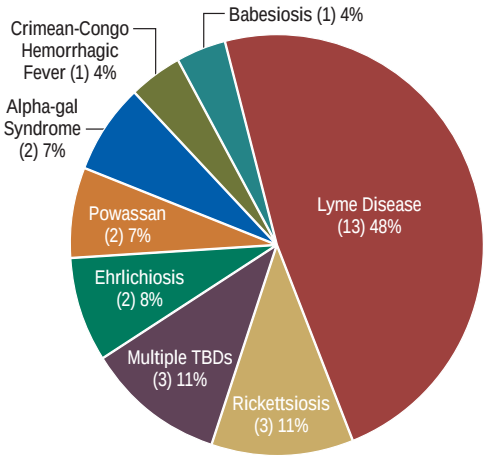
"After 10 years of misdiagnoses, I was finally diagnosed with Lyme disease and another TBD, babesiosis. Obtaining proper diagnosis and treatment is a challenge due to inadequate TBD diagnostics. I'm grateful that the CDMRP is addressing the many Americans infected with TBDs."
Lia Gaertner, M.S., Director of Education and Outreach at the Bay Area Lyme Foundation, TBDRP Consumer Reviewer

Overarching Challenges

Currently, there are at least 18 known infectious tick-borne pathogens, resulting in 20 conditions and 13 illnesses.[1] As tick populations increase and geographically expand, it is anticipated that new pathogens and conditions/illnesses associated with tick-bites will emerge,[2] and the number of annual cases of Lyme disease and other bacterial, viral, and parasitic TBDs will continue to rise.



FY16-FY19 TBDRP Portfolio Investment by Focus Area/SCS Code[3]



FY16-FY19 TBDRP Portfolio Investment by Disease Classification[3]

Continued research efforts are necessary to elucidate the mechanisms of tick-borne pathogen transmission, the human immune response to pathogens and pathogen immune evasion, the establishment of persistent infections and chronic clinical manifestations of disease, and the implications of co-infections on all of these complex processes. A need still exists for new and improved tick bite and TBD prevention strategies, as well as tick- and rodent-targeted infection prevention and control interventions. For those who are bitten, sensitive and specific assays for direct pathogen detection are vitally important, as they would ideally allow for tailored and rapidly initiated treatment plans for patients suffering acute infection to prevent the progression toward persistent infection and symptoms. The TBDRP intends to support researchers focused on development, validation, and translation efforts that will address these critical issues, improve the capabilities in the field of TBD prevention, diagnosis, and treatment, and ultimately benefit patients.

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

Program Goals and Strategy

The FY20 TBDRP offers award mechanisms for career and idea development to recruit new investigators mentored by established TBD scientists, support existing TBD researchers, and foster collaboration among fields. The TBDRP's vision places emphasis on burden of disease, and the program encourages investigators to focus their efforts on TBDs prevalent in the United States, of concern to military personnel and their beneficiaries in the US and overseas, and/or in understudied patient populations. Applications submitted to the TBDRP must address at least one of the following Focus Areas in Lyme disease and other TBDs: diagnosis, pathogenesis, prevention, and treatment. Current TBDRP-funded diagnosis research is focused on the sensitive, specific, and rapid detection of acute TBD infection, including development and optimization of innovative assays and biomarker panels. Pathogenesis studies in the portfolio include mechanistic studies to evaluate pathogen dissemination, epigenetic and transcriptomic changes defining pathology, host-immune responses to tick-borne infection, and neurologic symptoms linked to persistent infection. TBDRP prevention research spans tick- and reservoir-targeted prevention, prediction, and control interventions, as well as novel TBD pre-exposure prophylaxis and vaccine approaches. Research on novel treatments and therapeutic strategies addresses TBD symptoms and mitigation of long-term sequelae following TBD infection and includes antibiotic and non-antibiotic approaches.

Funded Investigator Perspective

Nicole Baumgarth, DVM, Ph.D., University of California, Davis

"Our laboratory aims to understand how Lyme disease-causing bacteria can survive and establish a persistent infection by evading the immune system. Our TBDRP-funded project uses a mouse model to understand why antibodies generated in response to infection can reduce, but not fully eliminate, infection and provide insight into human inability to clear infection. Defining the mechanistic differences between effective and non-effective antibodies can aid development of therapies that can overcome this limitation of the immune system and help patients return to health."

Kevin Esvelt, Ph.D., MIT

"Mice Against Ticks is a community-guided effort on the islands of Martha's Vineyard and Nantucket to prevent TBDs by disrupting disease transmission between white-footed mice and the ticks that feed on them. The TBDRP-funded portion of the study aims to isolate and characterize the best antibodies against Lyme bacteria and tick salivary components, as well as develop our genome insertion strategy and assess antibody production via pilot studies in mice. Our team has responsively adapted the project to local community needs toward a lasting solution for reducing the risk of human exposure to ticks."

Ulrike Munderloh, DVM, Ph.D., University of Minnesota

"The goal of our TBDRP-funded research is to develop a flexible, live vaccine platform against TBD agents that can quickly be modified by replacing or adding protective antigens from pathogens as they are recognized instead of having to develop new vaccines from the ground up. With a core component that is proven safe, this platform would dramatically shorten the time required for vaccine development, allowing more urgent deployment against a new or emerging TBD."

Yasuko Rikihisa, Ph.D., The Ohio State University

"Ehrlichia, the causative agent of human ehrlichiosis, is a member of the Rickettsiales order of bacteria, for which no human vaccines exist. Our TBDRP-funded award evaluates whether an ehrlichia surface protein is expressed in tick cells and can be blocked with antibodies in vitro to limit spread from tick to mammalian cells. In vivo studies aim to assess the ability of the ehrlichia surface protein-vaccine candidate to elicit a protective immune response against ehrlichia infection by tick bite and, if successful, could provide a prototype human rickettsiosis vaccine."

"The uniqueness of the TBDRP lies in the invaluable contributions of the advocates, who bring their own personal perspective and the voice of the advocacy groups they represent. Discussions greatly emphasize impactful research that promises to revolutionize the way that TBD patient care is managed. I have the greatest respect for the intellectual open-mindedness and for the plurality of views that I have encountered when serving as a TBDRP scientific reviewer."
Alessandra Luchini, Ph.D., TBDRP Scientific Peer Reviewer

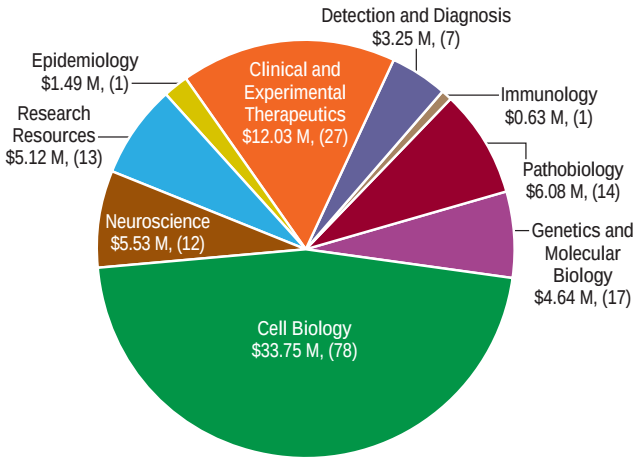
TUBEROUS SCLEROSIS COMPLEX RESEARCH PROGRAM

Program History

Tuberous sclerosis complex (TSC) is a genetic disorder that causes non-malignant tumors in many organs, primarily in the brain, eyes, heart, kidney, skin, and lungs. It has several clinical manifestations; however, seizures, developmental delay, intellectual disability, and autism have the greatest impact on quality of life. It is estimated that TSC affects approximately 50,000 individuals in the United States and 1 to 2 million individuals worldwide.

The Peer Reviewed Tuberous Sclerosis Complex Research Program (TSCRP) was established in FY02 when the efforts of TSC advocates led to a congressional appropriation of $1M to fund meritorious research for tuberous sclerosis. Since then, a total of $89M has been appropriated to the program, including $6M in FY20. Today, the TSCRP is one of the leading sources of extramural TSC research funding in the United States.

Since its inception, TSCRP has been supporting new ideas and investigators and has built a research portfolio of over 170 projects that include studies that span from promoting discoveries in TSC to further understand the many manifestations of the disease to clinical application.



FY02-FY19 TSCRP Portfolio Investment by SCS Code (Number of Awards)

Military Relevance

Seizures often result from TBI in military personnel, and according to the Defense Health Agency Medical Surveillance Monthly Report, 11,295 cases of epilepsy were reported among active duty Service members between 1998 and 2012.[1] In addition, in 2008, the DOD reported that 5,386 military dependents were diagnosed with ASD.[2] A substantial portion of the TSCRP-supported research is focusing on seizures and autism paving the way to finding cures and treatments for individuals with TSC and other neurological disorders that impact military Service members and their families.

Program Goals

While the ultimate goal of the TSCRP is to find a cure, the Program continues its efforts to improve prevention and treatment of TSC, focusing on the following goals:

- Eradicate tumors associated with TSC
- Prevent epilepsy, improve treatment, and mitigate co-morbidities associated with TSC-related seizures
- Understand the neurodevelopment features of TSC and reduce their impact

The TSCRP Strategic Plan can be found here:
http://cdmrp.army.mil/tscrp/pdfs/TSCRP%20Strategic%20Plan.pdf

[1] Epilepsy in active component service members, 1998-2012. 2013. *MSMR*. 2013 May; 20(5): 19-22.
[2] https://health.mil/search-results?query=autism

Vision: **Accelerate high-impact research to improve prevention strategies and treatments and to find a cure for TSC**

Mission: **Fund exploratory, pioneering, and transformative science that promotes discoveries in TSC, from mechanistic insights to clinical application across the lifespan, by supporting new ideas and investigators for the benefit of Service members, their beneficiaries, and the American public**

"There have been great leaps in the research and treatment options due to the work that we look to advance through the TSCRP. I am confident, when looking at what has been accomplished in this short time that we can, and will, have a significant, positive impact on those who struggle with the effects of TSC every day."
Matt Bolger,
TSCRP Consumer Peer Reviewer

Newly Funded Pilot Clinical Trials

Using Resting State Functional MRI to Find the Correct Surgical Target to Stop Seizures in TSC

Varina Boerwinkle, M.D., Phoenix Children's Hospital

Dr. Boerwinkle and her collaborators aim to improve surgical outcomes in children with epilepsy due to TSC in children using resting state functional MRI (RS fMRI) prior to surgery to identify the specific brain area(s) in which the seizures arise. They will assess whether this information affects surgical planning and also determine if the area was surgically removed, and if there were improved seizure outcomes. Furthermore, they will assess whether RS fMRI can identify abnormalities associated with language impairment in ASD and intellectual disability. In addition to Phoenix Children's Hospital, this study will also enroll patients at the Cincinnati Children's Hospital, and Texas Children's Hospital.

Using a Remote Caregiver Training to Improve the Social Engagement and Social Communication in Children with TSC

Connie Kasari, Ph.D., University of California, Los Angeles

This study, built on a previously funded TSCRP pilot clinical trial, will assess the therapist- and parent-mediated intervention JASPER (Joint Attention; Symbolic Play, Engagement, and Regulation) using a remote training program. In the adapted version of JASPER, called TSC Remote Assessment and Intervention (TRAIN), all training, after an initial in-person consultation, is provided remotely through weekly teleconferences and video feedback. The overall goal of this study is to determine if remote caregiver training can improve social engagement and communication between caregivers and their child with TSC.

Research Accomplishments

Combination Treatment of LAM in TSC

Elizabeth Henske, M.D., Brigham and Women's Hospital

Dr. Henske and Dr. Souheil El-Chemaly combined Sirolimus and hydroxychloroquine to treat Lymphangioleiomyomatosis (LAM) in TSC patients and in sporadic LAM patients. The results of this clinical trial demonstrated that the combination of these two drugs was well tolerated in women with LAM. In additional studies led by Dr. El-Chemaly and Dr. Carmen Priolo, they analyzed serum from women who participated in the clinical trial. They found that levels of serum methylthioadenosine (MTA), increased during treatment, making MTA a candidate biomarker for determining clinical response to the combination therapy. Moreover, they found that serum soluble vascular endothelial growth factor receptor (VEGFR)-3 and C-C motif chemokine ligand 21 (CCL21) levels decreased following the combination therapy. Both VEGFR-3 and CCL21 are closely linked to VEGF-D, the only current diagnostic biomarker for LAM. These results could provide more effective ways to diagnose, treat, and monitor LAM. Larger Phase II/III clinical trials to test the long-term effects and efficacy of this combination therapy may lead to improved quality of life for women with TSC and LAM.

Causes of Epilepsy in TSC-Potential Therapeutic Targets

Angelique Bordey, Ph.D., Yale University School of Medicine

Dr. Bordey and her team generated a novel mouse model of focal cortical malformation (FCM) in which Rheb, the activator of mTORC1, is constitutively active (RhebCA), resulting in the formation of cortical tubers similar to those associated with recurrent seizures in TSC patients. Using this model, they identified abnormal expression of a pacemaker channel, HCN4, in tuber neurons, which is not observed in a normal cortex and postulated that these channels are involved in TSC-related seizures. Furthermore, their data from the FCM model showed that HCN4 expression preceded the establishment of epilepsy, and it was also found in dysmorphic cortical neurons from TSC patients who underwent surgery for epilepsy treatment. Blocking the activation of the HCN4 channel using the HCN channel blocker, zatebradine, normalized resting membrane potentials of dysmprophic neurons in the FCM and decreased neuronal excitability. Finally, using a genetic approach by introducing nonfunctional HCN4 channels in this model prevented the occurrence of seizures. These results point to a novel mechanism of epileptogenesis and, moreover, suggest that gene therapy may be a treatment option to prevent seizure initiation in patients with TSC.

VISION RESEARCH PROGRAM

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

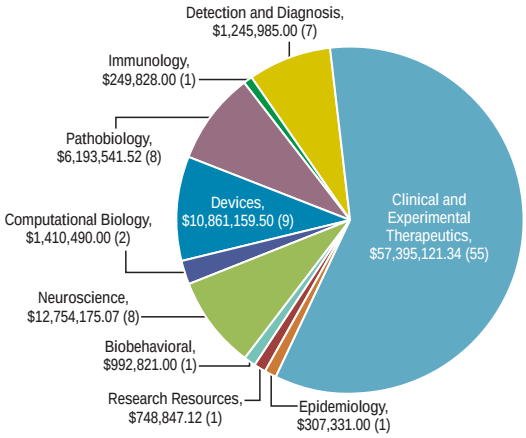
Mission: **To identify and address clinical needs through directed medical research to improve the health and readiness of military personnel affected by eye injuries and vision dysfunction**

"As a member of the Blinded Veterans Association, I feel a responsibility to serve as an ambassador and educator for not only blinded Veterans, but blind and visually impaired people in general. The VRP, has helped me learn about other forms of vision loss, connected me with top national researchers, given me a platform to share my personal challenges and experiences and restored in me a new found sense of purpose. Its mission and commitment to our military and Veterans is unparalleled."

Kennan Horn, VRP Consumer Reviewer

Program History

The DOD Peer Reviewed Vision Research Program (VRP) is the leading funder of research on visual system trauma, including injuries to the ocular system and visual dysfunction associated with TBI. The VRP was established in 2009 and has received annual appropriations totaling $124.95M through FY19. Research supported by the VRP spans the continuum of vision system trauma care, from point-of-injury and en route care to acute definitive care to chronic care and vision restoration.



FY09-FY19 VRP Portfolio Investment by SCS Code (Number of Awards)

Relevance to Military Health

Eye injury and visual dysfunction resulting from battlefield trauma affect a large number of Service members and Veterans. Surveillance data from the DOD indicate that eye injury accounts for approximately 15% of all injuries from battlefield trauma sustained during the wars in Afghanistan and Iraq, resulting in more than 182,000 ambulatory patients and 4,000 hospitalizations between 2000 and 2011. In addition, statistics from the Defense and Veterans Brain Injury Center show that through the first quarter of 2018, more than 380,000 Service members have been diagnosed with TBI, which can have significant impact on vision even when there is no injury to the eye. Research sponsored by the VA showed that as many as 75% of Service members who suffered a TBI have visual dysfunction, with some patients suffering vision loss and functional blindness.

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-relevant trauma, and research that will enable the delivery of care in the military operational environment.

Focus Areas

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

FY19 Focused Translational Team Science Award (FTTSA)

The VRP initiated the FTTSA mechanism in FY18 to support team initiatives that will fundamentally advance understanding and treatment of eye injury and/or visual dysfunction resulting from a military-relevant traumatic event. The FY19 recipient of the FTTSA is:

Outer Retina Reconstruction for Combat Afflictions (ORRCA)
David Gamm, M.D., Ph.D. (pictured), Zhenqiang Jack Ma, Ph.D., and Shaoqin Gong, Ph.D., McPherson Eye Research Institute, University of Wisconsin, Madison; Lt Col Richard Blanch, FRCOphth, Ph.D., University of Birmingham, UK; Kapil Bharti, Ph.D., National Eye Institute

Currently, there is no treatment for blinding retinal injuries caused by blunt force trauma or laser exposure. To reconstruct irreversibly damaged areas within the central outer retina, Dr. David Gamm has assembled a multidisciplinary, international team that together will develop a precision-based outer retinal cell replacement therapy. This team effort combines the production of retinal cells from induced pluripotent stem cells (led by Dr. Gamm), bioengineering of outer retina scaffolds for cell ensemble (led by Drs. Ma and Gong), and the development and optimization of surgical techniques in large animal models of blunt force injury and laser-induced injury (led by Lt Col Blanch and Dr. Bharti). If successful, this collaborative effort will advance an innovative cell replacement therapy to clinical testing and set the stage to change the standard of care for Service members and Veterans with blinding retinal injuries as well as civilians suffering from blinding retinal diseases.

Advancements in Surgical Interventions of Ocular Trauma

FY13 Translational Research Award

Novel Strategies for Optic Neuroregeneration and Retinal Projection Reintegration After Ocular Trauma
Vijay Gorantla, M.D., Ph.D., FRCS, Wake Forest School of Medicine; Larry Benowitz, Ph.D., Harvard University; Jeffrey Goldberg, M.D., Ph.D., Stanford University

Whole-eye transplantation (WET) holds the potential to restore vision following ischemic, traumatic, or degenerative damage to the optic nerve or eye. To study ocular immunology after WET, Drs. Gorantla, Benowitz, and Goldberg established first-in-class rodent and porcine WET models and two porcine models of crush and transection optic nerve injury, respectively. The investigators identified key regulatory molecules and therapeutic targets that enhance neuroprotection and regeneration, optimized WET techniques, and gained insight into inflammation and immune rejection after WET, thus helping researchers surmount the overarching obstacles to WET and facilitating the clinical translation of the best candidate interventions.

FY15 Technology/Therapeutic Development Award

Retinal Detachment Repair Without Tamponade by Thermofusion of the Retina and RPE for Rapid Vision Restoration and Safe Air Transport
Wilson Heriot, MBBS, FRACS, FRANZCO, Centre for Eye Research Australia Limited

Retinal detachment repair surgery often employs gas tamponade to prevent fluid flow through the retina break into the subretinal space. Problematically, gas tamponade may expand during air evacuation. Seeking an alternative procedure, Dr. Heriot has refined the protocol and device for retinal thermofusion (RTF), in which intraoperative sealing of the retinal tear margin is achieved by subretinal space dehydration prior to laser photocoagulation. The team has tested RTF in two large animal models and on ex vivo human donor eye tissue, with promising results. The successful application of RTF will not only enable immediate post-operative aeromedical evacuation but also reduce post-operative recovery time by simplifying surgical technique and equipment.

FY15 Technology/Therapeutic Development Award

Complex Orbital Reconstruction
Warren Grayson, Ph.D., Johns Hopkins University

On and off the battlefield, craniofacial injuries often involve a loss of maxillary and periorbital architecture and require numerous sequential complex surgeries. A critical need for improved surgical methods to achieve adequate aesthetic restoration or functional recovery led Dr. Grayson and his team to develop composite, vascularized bone grafts that can be 3D-printed into precise anatomical structures. The bone grafts were successfully used to regenerate vascularized bone in a mouse model of large craniofacial defect. Current efforts focus on repairing periorbital bone defect in a large animal model and Good Manufacturing Practice production of the grafts, setting the stage for clinical testing of this transformative technology that combines multi-tissue reconstruction and personalized medicine.

ADDITIONAL SUPPORTED DOD PROGRAMS/PROJECTS

CDMRP assists with management of certain aspects of programs managed by other offices. Some of the research managed by CDMRP for a few of these programs is highlighted here.

CLINICAL RESEARCH INTRAMURAL INITIATIVE

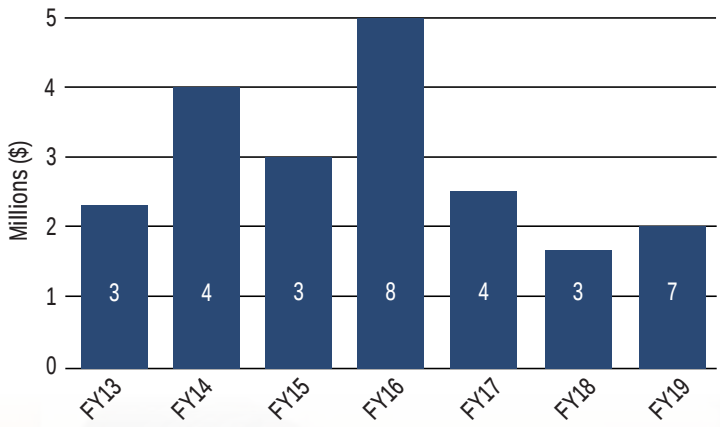
Mission: **To promote and support biomedical research at Military Treatment Facilities for the benefit of the Service Member, Veterans and beneficiaries**

Program History

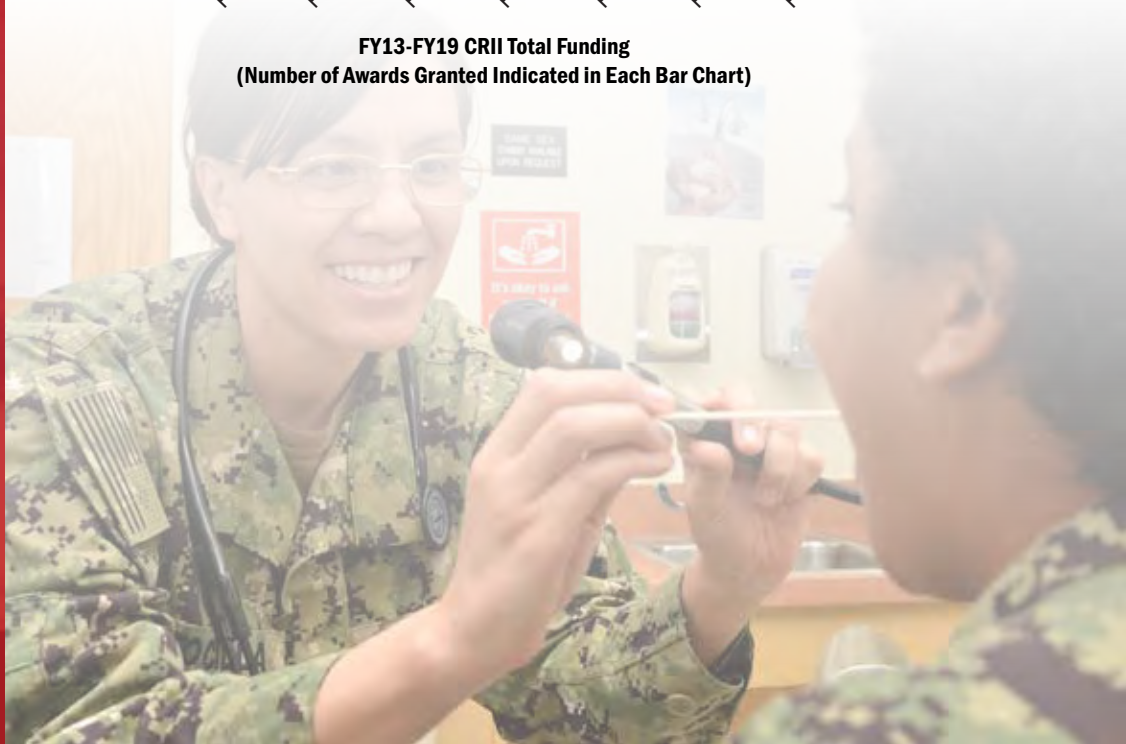
The Clinical Research Intramural Initiative (CRII) was established in 2012 to provide support for intramural clinical research in Office of the Assistant Secretary of Defense for Health Affairs (OASD[HA])-directed topic areas. The intent of the CRII is to foster intramural research aimed at protecting, supporting, and advancing the health and welfare of military personnel, families, and communities while supporting the development of military researchers and building Military Health Systems research capabilities. In addition to supporting intramural research, the CRII provides infrastructure support to MTFs under the DHP RDT&E.

Program Portfolio

The CRII has funded 32 awards through FY19, totaling approximately $20.4M to fund efforts in Intramural Initiated Research, Military Training Injuries, Health Services, Precision Medicine, Military Women's Health, Military Performance Optimization and Investigator Initiated Research.



FY13-FY19 CRII Total Funding
(Number of Awards Granted Indicated in Each Bar Chart)



CRII Awards Funded Through FY19

2013	Connectome Analysis of Distributed Neural Networks in Military TBI/PH	National Intrepid Center of Excellence
	Evaluation of Objective Assessments from Acute Combat-Related mTBI/Concussion Patients to Inform Return-to-Duty Guidance and Postconcussive Syndrome Risk	Naval Medical Center, Portsmouth, VA
	Human-Dog Interactions: Neuroendocrine and Physiological Alterations in Service Members with PTSD Who Train Service Dogs	Uniformed Services University of the Health Sciences
2014	Reducing Injuries with Training Enhancement, Targeted Rehabilitation, and Core Conditioning (RITE TRACC)	Uniformed Services University of the Health Sciences
	Enhancing the Success of Functional Restoration Using Integrative Therapies: Comparative Effectiveness Analysis in Active Duty Service Members with Chronic Pain	Madigan Army Medical Center
	Athletic Trainer Integration in US Air Force Basic Training: Reducing Injury and Related Costs	Wilford Hall Medical Center
	Optimization of Return to Duty and Outcomes in Military Training Shoulder and Knee Instability Injuries	Walter Reed National Military Medical Center
2015	Utility of Repetitive Transcranial Magnetic Stimulation (TMS) in Promoting Rapid Psychiatric Stabilization in Acutely Suicidal Military Service Members	Dwight David Eisenhower Army Medical Center
	Diabetes ROADMAP: An Intervention to Address Health Disparities Through Personalized Diagnosis Communication	Uniformed Services University of the Health Sciences
	Randomized Controlled Trial of a Sleep Study + Targeted CPAP Therapy for Obstructive Sleep Apnea to Reduce the Incidence of Adverse Pregnancy Outcomes	Naval Medical Center, San Diego
2016	Baseline Psychological Testing of Recruits	Wilford Hall Medical Center
	The Pap Smear Challenge: Comparing Clinical Performance of a Novel "Molecular Pap" Based on Next-Generation Sequencing to Traditional Cervical Cancer Screening	US Army Brooke Army Medical Center
	Evaluation of Multiple Potential Pharmacogenomic Risk Factors for Chronic Mefloquine Neurotoxicity Through the Establishment of a Drug Safety Registry	Uniformed Services University of the Health Sciences
	Genomics of Early Lung Cancer Among Military Personnel (GELCAMP)	Walter Reed National Military Medical Center
	Hearing Health Education Delivery Using a Precision Preventive Medicine Approach	Wilford Hall Medical Center
	Development of Clinical Decision Support Tools for Patients with Advanced Prostate Cancer	Uniformed Services University of the Health Sciences
	Defining Mutations of DNA Repair Genes in Prostate Cancer Patients Toward Enhancing Treatment	Uniformed Services University of the Health Sciences
	A Systems Biology Approach to Radiation Biodosimetry and the Host-Environment Interaction: Applications to Mass Casualty Triage in the Polytrauma Patient	US Army Institute of Surgical Research
2017	Evaluating the Use of Brain Stimulation to Enhance Neuroplasticity and Mitigate Cognitive Dysfunction Induced by Environmental Stressors in Female Rats	US Naval Medical Research Unit Dayton
	Early Screening and Diagnosis for Low Bone Mineral Density Utilizing Opportunistic Screening, Serum Biomarkers, and Advanced Modeling	Uniformed Services University of the Health Sciences
	Sleep Disorders in Military Women: Identifying Causal Factors and the Impact of Treatment on Psychological Health and Resilience	Wilford Hall Medical Center
	Optimizing Orthotic and Prosthetic Components for Military Women with Limb Salvage or Amputation	Naval Medical Center, San Diego
2018	Using Personal Light Treatment Devices to Improve Performance of Submariners	Naval Submarine Medical Research Laboratory
	Evaluating the Impact of a High-Intensity Cognitive Agility Optimization Intervention in Special Operations Forces: A Randomized Comparative Effectiveness Trial	Uniformed Services University of the Health Sciences
	Performance Optimization of Military Free Fall Instructors	Naval Health Research Center
2019	Antibacterial Effects of Extracellular Vesicles Released from Activated Mesenchymal Stem Cells in Models of Chronic Infection Associated with Biofilm Formation	Tripler Army Medical Center
	Development of Combination Therapy with Phage- and Biofilm-Disrupting Antimicrobial Peptides (AMPs) for Overcoming Multidrug-Resistant (MDR) Bacterial Infections	Naval Medical Research Center
	Visual Performance of Mild Color Vision-Deficient Military Aviators and Aircrew While Wearing Laser Eye Protection	US Naval Medical Research Unit Dayton
	Stem Cell and Biologic Therapies to Promote Tissue Regeneration and Function in Neuromusculoskeletal Trauma	Madigan Army Medical Center
	Efficacy of Oxygen-Carrying Therapeutic and Antioxidant Drug in Treatment of Cerebrovascular Complications as a Consequence of Severe Blast TBI	Naval Medical Research Center
	Virtual Reality Trauma Simulation: An Immersive Method to Enhance Medical Personnel Training and Readiness	Madigan Army Medical Center
	Therapeutic Microneedle Hydrogel for Burn Wound Field Care	US Army Institute of Surgical Research

DEFENSE MEDICAL RESEARCH AND DEVELOPMENT PROGRAM

Mission: To provide full life-cycle operational execution management support for Defense Health Program core research program areas in support of advancing collaborative, innovative medical research and development to improve military community health and save lives on and off the battlefield

Program History

As directed by the OASD(HA), the DHA J9, Research and Development Directorate manages and executes the DHP RDT&E appropriation. The USAMRDC CDMRP provides the Defense Medical Research and Development Program (DMRDP) execution management support for six DHP core research program areas, including:

- **Medical Simulation and Information Sciences**
- **Military Infectious Diseases**
- **Military Operational Medicine**
- **Combat Casualty Care**
- **Radiation Health Effects**
- **Clinical and Rehabilitative Medicine**

JPCs/PADs, which consist of DOD and non-DOD medical and military technical experts and representatives from the VA and HHS, provide strategic guidance for each of these major research program areas. Within USAMRDC, operational support responsibilities for the JPCs/PADs are provided by multiple execution agents, including CDMRP, individual laboratories, and advanced developers. In partnership with the JPCs/PADs, CDMRP supports development of funding opportunities, solicitation and review of applications, full life-cycle management of awards, and program evaluation and planning.

Program and Portfolio Areas

From FY10-FY19, CDMRP helped to manage approximately $914.7M invested in DMRDP awards ranging across basic, translational, and clinical research efforts. CDMRP also supported cross-cutting initiatives through DMRDP such as Accelerating Innovation in Military Medicine and the Clinical Research Intramural Initiative. In addition, CDMRP began providing management support for Other Transaction Agreements (OTAs) in FY19, including those funded through USAMRDC's Medical Technology Enterprise Consortium OTA.

Across all areas, these projects have the potential to yield critical prevention, detection, diagnosis, treatment, and rehabilitation and reintegration strategies for the nation's Service members, Veterans, and their family members. Information on the DHA R&D core research programs and recent research projects is listed on the following DMRDP pages.

Medical Simulation and Information Sciences Research Program (MSISRP)

MSISRP plans, coordinates, and oversees three portfolios of research: (1) Medical Simulation (MedSim), focused on improving military medical training through medical modeling, simulation, educational gaming, assessment systems, interoperable training platforms, and objective training metrics; (2) Health Information Technologies/ Informatics (HITI), focused on developing, researching, and/or improving technologies and informatics that support Theater and Operational Medicine, such as the capture, movement, storage, usability, use, and sharing of health-related data for better clinical care, strategic planning, process development, and software applications and (3) Medical Assist Support Technologies (MAST) focused on future medical systems and approaches that optimize medical care delivery and the reduction of the medical logistics footprint in support of multi-domain operations wherein challenges due to far-forward and dispersed geographic environments and shortfalls in both human and materiel resources can be experienced.

MSISRP's mission is to execute medical science and technology programs to strategically bridge gaps in capabilities by creating and developing emerging and disruptive military medical capabilities with a focus on full lifecycle impact and integration of its research activities. The MSISRP works with all the Services and joint agencies to address gaps, threats, and requirements as identified by the Military Health System.

Additional information about MSISRP is available at: https://mrdc.amedd.army.mil/index.cfm?pageid=medical_r_and_d.msisi.overview

Recent MSISRP DHP Research

- Trauma Resiliency Immersive Adaptive Gaming Environment (TRIAGE) Award – *Rodney Metoyer at BioMojo, LLC*
- Foundational Research for Autonomous, Unmanned, and Robotics Development of Medical Technologies – *George Kramer at the University of Texas Medical Branch - Galveston*

Military Infectious Diseases Research Program (MIDRP)

MIDRP supports R&D, leading to the fielding of effective, improved means of bacterial, parasitic, and viral infection prevention, screening, diagnosis, and treatment to maintain maximal global operational capability with minimal morbidity and mortality. MIDRP's DHA-aligned, CDMRP-supported mission is focused on the following research area:

- Bacterial Diseases

The goal of the Bacterial Diseases portfolio is to identify and develop novel approaches to prevent, diagnose, manage, and treat combat wound infections. Under the Bacterial Diseases task area, CDMRP supports MIDRP's DHP core research program-aligned projects within the subtask area of Wound Infection. Supported research efforts are focused on development of host immune response and pathogen biomarkers associated with infection to inform clinical wound-management decisions, development of tools for early detection of drug resistant organisms causing wound infections, and development of novel therapeutics and innovative delivery technologies against wound infection pathogen and biofilm processes. The research supported under these task areas spans basic research on multi-drug resistant bacteria and fungi, as well as biofilm formation; prevention, diagnosis, and treatment of bacterial and fungal wound infections; and development of pre-clinical animal models for therapeutics development. Additional information about MIDRP is available at: https://midrp.amedd.army.mil/info/PGAreas.jsp.

Recent MIDRP DHP Research

- Development of a Novel Antibiotic Targeting Multi-Drug-Resistant Staphylococcus Aureus - *Andrea Stierle at The University of Montana*
- Standard-Issue Copper-Based Antimicrobial Military Wound Dressing - *Aaron Strickland at iFyber, LLC*
- IND-Enablement of Kinocidin Gamma-RP-1 for MDR Gram-Negative Infections - *Michael Yeaman at Lundquist Institute for Biomedical Innovation at Harbor-UCLA Medical*

Military Operational Medicine Research Program (MOMRP)

MOMRP seeks to develop effective countermeasures against stressors and to maximize health, performance, and well-being. MOMRP conducts biomedical research to deliver products and solutions to the Warrior that address health and fitness throughout the deployment cycle. MOMRP is centered on cutting-edge scientific research and bringing science to the Soldier on the battlefield in a relevant, timely manner by focusing on the following research areas:

- Injury Prevention and Reduction
- Psychological Health and Resilience
- Physiological Health
- Environmental Health and Protection

Each area represents efforts to develop guidelines and criteria to predict, prevent, and mitigate physical and psychological injury and contribute to the shared responsibility of enabling our Armed Forces and providing them with the best care possible. Additional information about MOMRP can be found at https://momrp.amedd.army.mil/.

Recent MOMRP DHP Research

- Brief Cognitive Behavioral Therapy (BCBT) Replication Trial - *Craig Bryan, University of Utah*
- Dense Urban Environment Dosimetry for Actionable Information and Recording Exposure (DUE DARE) – *David Lary at the University of Texas at Dallas*
- Investigating Striatal Attentional Circuits to Understand and Mitigate Deficits in Cognitive Flexibility Due to Sleep Loss – *Hans Van Dongen at Washington State University, Pullman*

Combat Casualty Care Research Program (CCCRP)

CCCRP seeks to drive medical innovation through development of knowledge and materiel solutions for the acute and early management of combat-related trauma, including point-of-injury, en route, and facility-based care. CCCRP strives to optimize survival and recovery from combat-related injury by targeting the following research areas:

- Prolonged Field Care
- Battlefield Resuscitation and Immediate Stabilization of Combat Casualties
- En Route Care
- Neurotrauma and Traumatic Brain Injury

Research planned, programmed, and managed by CCCRP is gap-driven and motivated by the urgency to generate solutions (clinical practice guidelines or FDA-approved products) to benefit the Warfighter and the American public. CCCRP supports the complete range of research activities needed to achieve its goals, from foundational science to improvements in healthcare services and delivery. Additional information about CCCRP can be found at https://ccc.amedd.army.mil.

Recent CCCRP DHP Research

- Freeze Dried Platelet Extracellular Vesicles as a Hemostatic Adjunct to Resuscitation for Prolonged Field Care - *Shibani Pati at the University of California San Francisco*
- Advanced Technology Development for a Secure Wireless Disposable Physiological Monitoring Patch - *Brian Stancil at Lifeware Labs, LLC*
- Skin Grafting from 9-Gene Genetically Engineered Pigs in the Treatment of Burns: An Experimental Study in Monkeys - *Takayuki Yamamoto at the University of Alabama Birmingham*

Radiation Health Effects Research Program (RHERP)

RHERP seeks to develop medical countermeasures for acute ionizing radiation injury. Research areas include post-exposure mitigation of radiation injury, prophylactic pharmaceutical solutions to prevent injury from ionizing radiation, understanding the mechanisms of radiation injury, and development of novel biodosimetry tools. Currently, DHP research sponsored by RHERP is focused on the following key area:

- Biomedical Technology for Radiation Countermeasures

Recent RHERP DHP Research

- Anticeramide scFv as Prophylaxis of the Radiation GI Syndrom - *Zvi Fuks at Ceramedix Holding LLC (JWMRP funded)*

Clinical and Rehabilitative Medicine Research Program (CRMRP)

CRMRP prioritizes research efforts based on the types of injuries and degree of trauma suffered by Warfighters, while tracking current state-of-the-art technologies. CRMRP innovations are expected to improve restorative treatments and rehabilitative care to maximize function for return to duty or civilian life. The priorities for funding research efforts are closely coordinated with other Services, partner agencies, and industry to help ensure a diverse portfolio with targeted Focus Areas to meet current needs. Currently, research sponsored by CRMRP is focused on the following key areas:

- Neuromusculoskeletal Injury Rehabilitation
- Pain Management
- Regenerative Medicine
- Sensory System Traumatic Injury (visual, auditory, and vestibular dysfunction)

CRMRP's mission is to implement long-term strategies to develop knowledge and materiel products to reconstruct, rehabilitate, and provide definitive care for injured Service members. The ultimate goal is to return the Service member to duty and restore their quality of life. Additional information about CRMRP can be found at https://mrdc.amedd.army.mil/index.cfm/program_areas/medical_research_and_development/crmrp_overview.

Recent CRMRP DHP Research

- Adenosine 3A Receptor Agonists for the Treatment of Neuropathic Pain – *Gary Bennett at BioIntervene, Inc.*
- Natural Sensation of Foot-Floor Interactions for Transfemoral Amputees via Neural Stimulation – *Ronald Triolo at Case Western Reserve University*
- Multi-Center Phase II Trial to Test Ability for Stem Cell Therapy to Induce Palmo-Plantar Skin at the Stump Site of Amputees – *Luis Garza at Johns Hopkins University*

A number of CDMRP-managed congressional programs fund research that is highly relevant to the DOD and Army core research program areas. CDMRP coordinates closely with JPC/PAD staff, product developers, and others within the DOD to identify and address relevant gaps and maximize the dividends for the DOD from research funded in these areas.

Programs include:

- ASADRP
- CPMRP
- CRRP
- ERP
- GWIRP
- HRRP
- JWMRP
- MBRP
- NETPR
- OPORP
- PRARP
- PRCRP
- PRMRP
- PRORP
- RTRP
- SCIRP
- TBDRP
- VRP

PSYCHOLOGICAL HEALTH AND TRAUMATIC BRAIN INJURY RESEARCH PROGRAM

Vision: **To prevent, mitigate, and treat the effects of traumatic stress and traumatic brain injury on function, wellness, and overall quality of life for Service members as well as their caregivers and families**

Mission: **Establish, fund, and integrate both individual and multiagency research efforts that will lead to improved prevention, detection, and treatment of PH/TBI**

Program History

Through FY19, CDMRP has managed 591 Peer Reviewed Psychological Health and Traumatic Brain Injury Research Program (PH/TBIRP) awards, totaling over $1,097.3M for projects ranging from basic to translational research across a wide range of Focus Areas, including screening, detection, diagnosis, treatment and intervention, neurobiology and genetics, prevention, families and caregivers, epidemiology, physics of blast, rehabilitation and reintegration, neuroprotection and repair, clinical management, and field epidemiology.

More information about PH/TBI supported initiatives can be found at:

- Consortia – (http://cdmrp.army.mil/phtbi/consortium/phtbictc)
- Research Resources – includes guidance, databases, methods, and repositories (http://cdmrp.army.mil/phtbi/resources/phtbiresources)

PH/TBIRP was established by Congress in FY07 in response to the devastating impact of TBI and psychological health (PH) issues, including PTSD, on our deployed Service members in Iraq and Afghanistan. Appropriations totaling $300M, $150M each for TBI and PH (including PTSD), were assigned to CDMRP for the purpose of soliciting and managing critical TBI- and PH-related R&D efforts to benefit Service members, Veterans, and other beneficiaries of the Military Health System. Additional congressional appropriations for PH/TBIRP were assigned to USAMRDC between FY09 and FY19, and a modified execution model was established in which strategic oversight is provided by USAMRDC-based research program areas aligned with the OASD(HA). As directed by the OASD(HA), the DHA J9, Research and Development Directorate manages and executes the DHP RDT&E appropriation, which includes the PH/TBIRP. The DHA J9, Research and Development Directorate leverages PH/TBIRP funding to support ongoing R&D in DHP research program areas relevant to PH and TBI.

The JPCs/PADs provide recommendations to the DHA J9, Research and Development Directorate, on research gaps, Focus Areas, and funding options for the PH/TBIRP. CDMRP works in partnership with DHA and the JPCs/PADs to provide operational execution management support as needed for PH/TBIRP, including development of funding opportunities, solicitation and review of applications, full life-cycle management of awards, and program evaluation and planning. The CDMRP-managed application review for PH/TBIRP follows a two-tier model, in which consumer involvement continues to be a hallmark. Our nation's Wounded Warriors typically serve in this capacity for PH/TBIRP, representing fellow Service members and Veterans to help identify the most relevant and impactful research. The modified execution process allows greater flexibility for aligning PH/TBIRP Congressional Special Interest funds to complement core DOD R&D efforts and address Military Health System needs.

PH/TBIRP Recent Research Focus

Research supported by the DOD's PH/TBIRP extends and complements ongoing DOD efforts toward promoting a better standard of care for PH (including PTSD), TBI, and related comorbidities in the areas of prevention, detection, diagnosis, treatment, and rehabilitation.

MOMRP

- Prospective Cohort Study of Stellate Ganglion Block for Treatment of Posttraumatic Stress Disorder Symptoms and Other Non-Pain Conditions – *Kristine Rae Olmsted, Research Triangle Institute*
- Adjustment Disorders in the US Military: Addressing Gaps in Knowledge and Practice – *Jouhayna Bajjani-Gebara, Uniformed Services University/Henry M Jackson Foundation*
- Enhanced Access, Acknowledge, Act at US Air Force Academy: Intervention with the Fourth Degree Classes of Cadets – *John Riley, US Air Force Academy*

CCCRP

- Rapid Ketone Infusion to Prevent Brain Energy Depletion and Secondary Brain Injury in Severe TBI with Hemorrhagic Shock – *Jennifer McGuire at the University of Cincinnati*
- Sex Differences in Cognitive and Mental Health Functioning Following Mild Traumatic Brain Injury – *Amy Jak at the Veterans Medical Research Foundation of San Diego*
- MR Imaging Biomarkers of Microstructure Relating to Cognitive Performance After Mild Traumatic Brain Injury – *Yvonne Lui at the New York University School of Medicine*

CRMRP

- Treatment of Verbal Retrieval Deficits in Mild Traumatic Brain Injury with High Definition Transcranial Direct Current Stimulation – *John Hart at University of Texas, Dallas*
- A Pragmatic Rehabilitation Intervention to Supplement Progressive Return to Activity Following Mild Traumatic Brain Injury in Service Members (SMs): The Active Rehab Study – *Johna Register-Mihalik at University of North Carolina, Chapel Hill*
- Control Network Neuromodulation to Enhance Cognitive Training in Complex Traumatic Brain Injury (The CONNECT-TBI Trial) – *Davin Quinn at University of New Mexico Health Sciences Center*

SMALL BUSINESS INNOVATION RESEARCH AND SMALL BUSINESS TECHNOLOGY TRANSFER PROGRAMS

Vision: **To advance health and medical solutions toward commercialization to benefit Warfighters and their families**

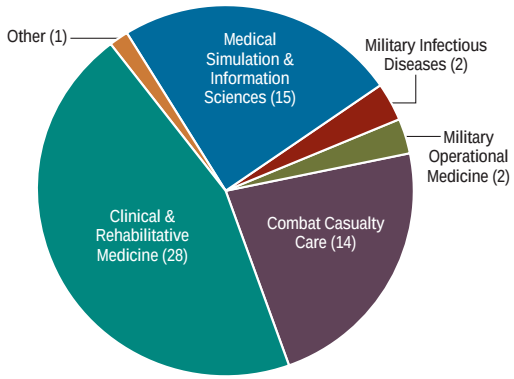
Mission: **To address military medicine needs through topic development and management oversight of R&D projects, in support of broader SBIR/STTR goals**

Program History

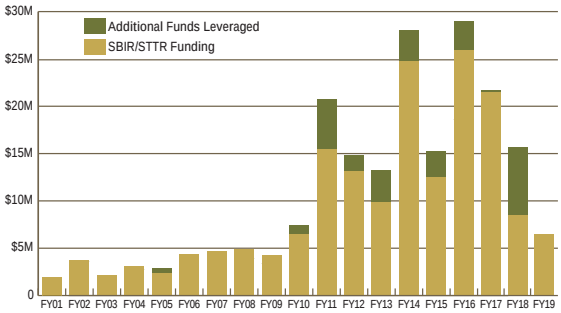
Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) are highly competitive programs that encourage US small businesses to engage in R&D with the incentive to profit from the product's commercialization. The programs are organized in three phases: Phase I establishes project feasibility; Phase II develops a prototype; and Phase III supports commercialization. SBIR/STTR funding is available for Phase I and Phase II; Phase III support requires non-SBIR/STTR funding sources.

CDMRP has leveraged SBIR and STTR funding since FY00 and FY04, respectively, to address unmet military needs. CDMRP collaborates closely with the JPCs and PADs at USAMRDC to develop topics in support of four distinct SBIR/STTR programs: Army SBIR, Army STTR, DHA SBIR, and DHA STTR. In addition to providing project management oversight, CDMRP personnel review proposals on behalf of the programs and support the projects through all phases of development.

Approved DOD SBIR and STTR topics are announced online at https://www.dodsbirsttr.mil/submissions/baa-schedule/active-baa-announcements.



FY12-FY20 CDMRP Topics by Program Area



Total SBIR/STTR Funds Managed by CDMRP

SBIR/STTR Projects Advancing Through the Phases

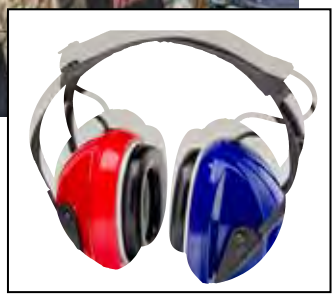
Topic Solicitation Year	Topics Managed by CDMRP	Phase I Awards	Phase II Awards	Additional Funding*
2012	9	30	9	4
2013	10	17	15	1
2014	2	6	4	2
2015	9	22	13	5
2016	7	19	12	3
2017	8	25	15	1
2018	4	10	5	0
2019	11	33	0	0
Totals	60	162	73	16

* Includes 2nd Phase II, Phase II Enhancement, and Phase III awards.

Highlights

Hearing Fitness for Duty and Return-to-Duty Assessment and Validation

Hearing loss is one of the most common health issues for Service members and Veterans, as hearing ability can become compromised from prolonged and acute noise exposure in operational environments. Hearing loss may inhibit Warfighter performance in missions where hearing ability is essential but current hearing tests do not adequately assess functional hearing capability.



In a Phase III SBIR project, building upon previous Army, Navy, and NIH SBIR investments to Creare, LLC., Dr. Clavier and DOD collaborators have developed novel tools, the Military Hearing In Noise Test (MHINT), and the Military Sound in Noise Test (MilSINT) to assess functional hearing. The MHINT involves presenting common military, and operationally relevant, phrases to examine speech-in-noise hearing performance. The MilSINT measures both detection and recognition of non-speech sounds. The tests are administered on hand-held mobile tablets that connect wirelessly to a noise attenuating audiometric headset that makes it possible to perform the tests outside of a booth, even in field-forward environments.

The team demonstrated that MHINT can be administered efficiently among Navy and Army personnel within varied settings. The work also developed return-to-duty hearing tests which could be incorporated into existing military fit-for-duty assessments after TBI. Improvements in hearing assessments have the potential to facilitate the development of mission-related standards for measuring functional hearing ability in the Warfighter.

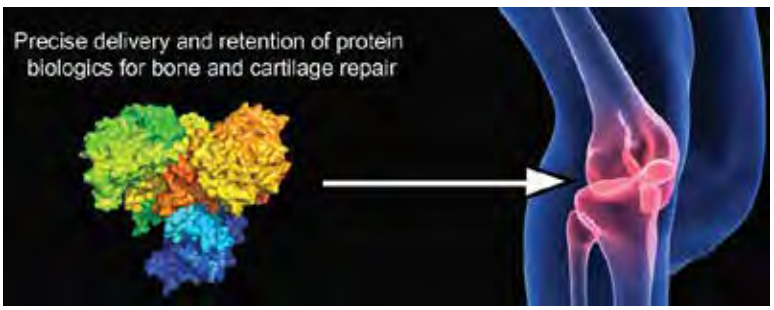
Developments from this work have become part of the Integrated Platform for Clinical Assessment and Monitoring system, which is now commercially available as an FDA-approved device through Creare's manufacturing arm, Edare.

Precise Tissue Regeneration with Persistent Targeting of Biologics

Precise tissue regeneration is one of the most challenging problems facing modern medicine. The US military faces the problem of how to speed return to duty following injury during both peacetime and combat. The issue here is the inability to control how the body heals itself. If it were possible to deliver potent bioactive proteins to injury sites without diffusion or off-target effects, then it would be possible to safely regenerate injured tissues.

Theradaptive developed a platform that converts recombinant proteins into variants that adhere to implant materials nearly irreversibly, like a paint. Using this technology, it is now possible to convert an inert implant into a bioactive implant. The company has developed bio-devices that can regenerate bone and cartilage with precision. The bone regenerative therapeutic has beaten the standard of care in all studies conducted to date.

Theradaptive leveraged Phase I, II, and IIE of a DHA SBIR to develop ConForma, a biphasic osteo-chondral repair implant that eliminates the need for autologous harvest and donor site pain. The ConForma implant is shelf-stable, cell therapy friendly, and leverages the biologic binding platform to deliver chondrogenic and osteogenic proteins in a persistent way. ConForma has consistently regenerated both bone and cartilage in preclinical studies.



The company is heading into human clinical studies for trauma repair, spinal fusion, and cartilage repair, with the first study starting in 2021. This platform technology opens the way to a wide array of biodevices that can transform the treatment of trauma and tissue degeneration.

TRAUMA CLINICAL RESEARCH PROGRAM

Program History

Trauma Clinical Research Program (TCRP) was initiated in FY16 to sustain and continue the hard-earned advances in military trauma research from the 15+ years of conflict in Iraq and Afghanistan. Since FY16, Congress has invested $10M per year to the TCRP. The FY16-FY17 appropriations were assigned to the CDMRP for management and execution in partnership with the USAMRDC CCCRP. In FY18, strategic oversight of the TCRP transferred to the CCCRP, and the CDMRP provides both technical and award management support.

Vision: **Improve treatment and outcomes in both military and civilian trauma**

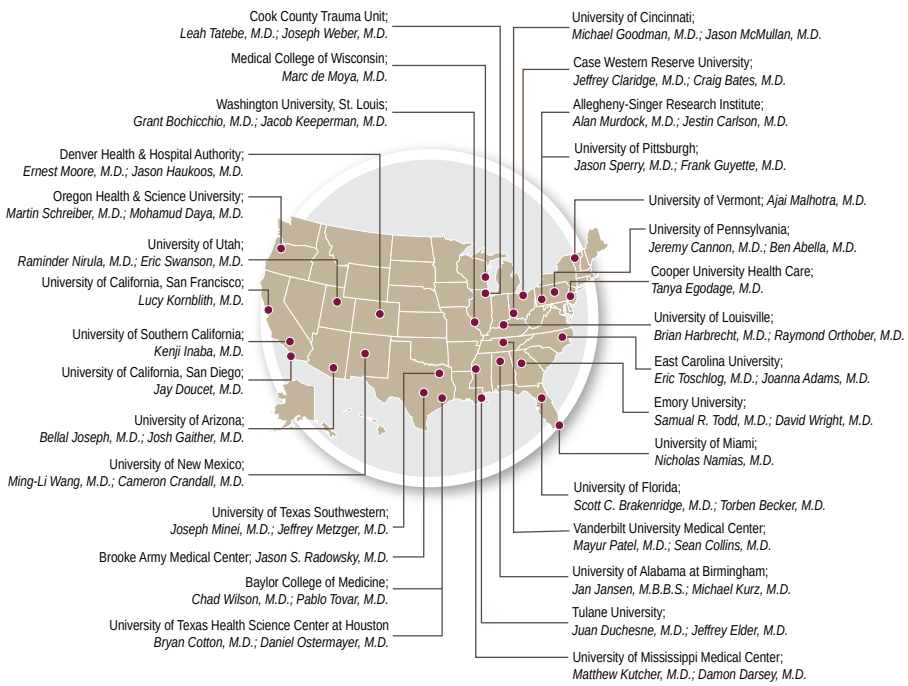
Mission: **To address the military relevant priorities and gaps in trauma care and facilitate the transition of lessons learned into best practice guidance and products**

Linking Investigations in Trauma and Emergency Services

Since FY16, TCRP congressional appropriations have supported the Linking Investigations in Trauma and Emergency Services (LITES) contract. The LITES contract is awarded to the University of Pittsburgh and establishes a multi-institution clinical research network of civilian trauma systems and medical research centers to address military-relevant priorities and gaps in trauma care. The LITES contract is not a singular research effort. Through the task order generation process, independent research studies or analyses can be performed by the LITES network. Each LITES Task Order is unique, and sites are selected for participation based on the objectives of the specific Task Order and the site's readiness to participate. As of May 2020, there are 31 LITES Network Sites and additional information is located on the LITES Network website (www.litesnetwork.org).

LITES Network

Site Principal Investigators



TASK ORDER #01

Eight sites within the LITES network are performing an inaugural, large, national, 5-year, prospective, multicenter observational cohort study to characterize the epidemiology of moderate and severe physical injury in the US, investigate regional variations of presenting characteristics, management practices, and attributable outcomes. It will also aim to determine and characterize injury-related factors, management practices, and trauma system factors resulting in or associated with preventable mortality. The study has the potential to promote new clinical practice guidelines and modify or update existing trauma standards of care for both military and civilian populations. As of May 2020, data has been collected on approximately 47,211 subjects, with a target of 60,000. The interim analysis has been reached. Efforts are underway to clean and analyze the massive amounts of Trauma Quality Improvement Program (TQIP), pre-hospital, and in-hospital data.

TASK ORDER #02: Shock, Whole Blood, and Assessment of TBI (SWAT)

SWAT is a multicenter, prospective, observational cohort study to determine the impact of whole blood resuscitation in trauma patients with hemorrhagic shock at risk of large volume resuscitation. Early whole blood resuscitation will be compared to standard component resuscitation at seven sites within the LITES network. This project will also look at how these two types of blood resuscitation compare in people with TBI. The project subject enrollment is 892 and as of May 2020, 510 subjects have been enrolled and interim analysis has begun. To optimize enrollment and promote balance between the whole blood and component groups, enrollment has been closed at one low-enrolling component therapy site and completed Site Initiation Visits at two new component therapy sites. The two new sites are anticipated to be open to enrollment late Quarter 2 to early Quarter 3 2020.

TASK ORDER #04: Cold Stored Platelet Early Intervention (CriSP) Trial

Resuscitation strategies for the acutely injured patient in hemorrhagic shock have evolved, with patients benefitting from receiving less crystalloid and early red blood cell use with balanced ratios of plasma and platelets. Despite these changes, deaths from traumatic hemorrhage continue to occur in the first hours following arrival at the trauma center, underscoring the importance of early interventions that provide benefit. The objective for this pilot trial is to determine the feasibility, efficacy, and safety of urgent release cold stored platelets in patients in hemorrhagic shock (CriSP-HS). This is a multi-center, open label, randomized trial that will enroll approximately 200 patients over a 2-year period and will utilize five sites within the LITES network. A second cohort of 100 subjects with TBI will be enrolled at the University of Pittsburgh in collaboration with the Department of Neurosurgery. FDA IND approval for the use of cold-stored platelets in hemorrhagic shock has been received and the submission of a Protocol Amendment to extend the use to TBI is in process. Initial IRB applications for both protocols are also underway.

TASK ORDER #05: Prehospital Airway Control Trial (PACT)

Prehospital trauma airway management is a low-frequency, high-consequence event for both military and civilian providers. Currently, prehospital providers typically use one of two methods to help people breathe: one is with a tube in the windpipe, called an endotracheal tube, and the other is with a device that sits over the windpipe, called a supraglottic airway. Although both methods currently used, it is unknown which is better. PACT is a proposed 5-year, open label, multi-center trial comparing standard strategies of definitive airway management to a strategy of initial supraglottic airways in trauma patients within the prehospital setting. 2,040 subjects will be enrolled across 20-30 prehospital agencies from eight sites within the LITES network.

TASK ORDER #06: Prehospital Analgesia INterventional (PAIN) trial

The objective is to perform a multicenter, randomized, double-blind, interventional trial of prehospital administration of ketamine versus fentanyl in injured patients at risk of hemorrhage or compensated shock. Prehospital pain management following traumatic injury in patients at risk of hemorrhage or compensated shock requires the ability to provide adequate pain management while avoiding the risks associated with analgesia. Among injured civilian and military personnel, opioids are the most common intervention for prehospital pain management. The trial will be carried out at seven sites within the LITES Network and enroll 1,544 subjects over 3 years. The Coordinating Center is having ongoing communication with the FDA to obtain an IND under Exception from Informed Consent.

APPENDIX A: FY92-FY19

Table A-1. Overview of Appropriations, Applications Received, and Awards Made for FY92-FY19

Programs Managed by CDMRP	Fiscal Year	Appropriations Received (in millions)	Applications Received	Applications Funded[1]
Alcohol and Substance Abuse Disorders[1]	2014-2019	$24.0	12	7
Amyotrophic Lateral Sclerosis	2007, 2009-2019	$89.4	621	84
Autism	2007-2019	$89.4	1,474	168
Bone Marrow Failure	2008-2019	$38.6	523	77
Breast Cancer	1992-2019	$3,641.3	58,898	6,980
Breast Cancer Research Semipostal[2]	1999-2019	$26.6	0	53
Chronic Myelogenous Leukemia	2002-2007	$22.1	252	61
Chronic Pain Management	2019	$10.0	54	7
Combat Readiness Medical Research	2019	$15.0	170	8
Defense Women's Health	1995	$40.0	559	69
Deployment Related Medical[1]	2008-2013	$101.9	1,094	58
DOD/VA	1999-2000	$6.8	88	9
Duchenne Muscular Dystrophy	2011-2019	$29.6	210	37
Epilepsy	2015-2019	$37.5	175	39
Genetic Studies of Food Allergies	2009-2010	$4.4	60	9
Gulf War Illness	2006, 2008-2019	$192.0	643	201
Hearing Restoration	2017-2019	$30.0	85	24
Institutionally Based Programs[1]	1995-2010	$486.3	306	501
Joint Warfighter Medical[1]	2012-2019	$354.0	237	85
Kidney Cancer	2017-2019	$45.0	646	84
Lung Cancer	2009-2019	$141.5	3,635	282
Lupus	2017-2019	$15.0	342	38
Melanoma	2019	$10.0	187	19
Military Burn[1]	2014-2019	$48.0	124	50
Multiple Sclerosis	2009-2019	$57.1	830	111
Myeloproliferative Disorders Research	2004	$4.3	18	9
National Prion Research Project	2002	$42.5	136	38
Neurofibromatosis	1996-2019	$347.9	1,703	430
Orthotics and Prosthetics Outcomes	2014-2019	$60.0	274	56
Osteoporosis	1995	$5.0	105	5
Ovarian Cancer	1997-2019	$336.5	4,071	479
Neurotoxin Exposure Treatment Parkinson's[1]	2014-2019	$96.0	445	113
Peer Reviewed Alzheimer's[1]	2014-2019	$84.0	585	129
Peer Reviewed Cancer	2009-2019	$429.8	5,352	736
Peer Reviewed Medical	1999-2006, 2008-2019	$2,350.7	14,246	1,601
Peer Reviewed Orthopaedic	2009-2019	$398.5	1,370	294
Prostate Cancer	1997-2019	$1,820.0	19,457	3,461
Reconstructive Transplant	2015-2019	$63.0	619	108

Continued on next page.

Table A-1. Overview of Appropriations, Applications Received, and Awards Made for FY92-FY19 (cont.)

Programs Managed by CDMRP	Fiscal Year	Appropriations Received (in millions)	Applications Received	Applications Funded[1]
Spinal Cord Injury	2009-2019	$277.9	1,284	255
Tick-Borne Disease	2016-2019	$20.0	201	27
Trauma Clinical Research Repository	2014	$5.0	3	1
Tuberous Sclerosis	2002-2006, 2008-2019	$83.0	788	170
Vision	2013-2019	$88.9	461	91
Miscellaneous				23
Additional Supported DOD Programs/Projects				
Armed Forces Institute of Regenerative Medicine II[3]	2017-2019	$30.8	-	-
Centers of Excellence	2015-2017	$17.2	-	1
Defense Medical Research and Development[4]	2010-2019	$914.7	2,179	589
Defense Medical Research and Development Congressional Special Interest Restoral[5]	2015-2019	$222.1	-	136
Psychological Health/Traumatic Brain Injury	2007, 2009-2019	$1,097.3	3,633	591
Rapid Innovation Fund	2011-2015	$35.7	-	15
Small Business Innovation Research/Small Business Technology Transfer	2014-2019	$93.2	179	241
Trauma Clinical	2016-2019	$40.0	-	-
Vision Prosthesis	2015-2016	$1.2	-	3
Other Submission Processes				
MRMC - Broad Agency Announcement[6]		-	595	-
Total		**$14,520.7**	**128,929**	**18,663**

[1] Includes awards transitioned to CDMRP with the merger.
[2] Breast Cancer Research Semipostal funds applications received and reviewed by the Breast Cancer Research Program. BCRS contributed to 73 awards; 45 fully funded and 28 partially funded.
[3] Armed Forces Institute of Regenerative Medicine II FY19 appropriations were used to fund 6 modifications.
[4] Includes 2013-2015 Clinical Research Intramural Initiative and 2010 Chiropractic Clinical Trials.
[5] Includes 2016-2019 Clinical Research Intramural Initiative.
[6] CDMRP manages the application receipt and review process for the USAMRMC Broad Agency Announcement. Proposals that are funded are counted in the program that provided the funding. Of the 295 applications received, CDMRP funded 46.

APPENDIX B: FY19-FY20

Table B-1. FY19-FY20 Alcohol and Substance Abuse Research Program Congressional Language and Appropriations, Withholds and Management Costs, and Execution of Investment Strategy

Fiscal Year	Congressional Language and Appropriations	Withholds and Management Costs	Investment Strategy
2019	**$4M** for Alcohol and Substance Abuse Research	**Withholds** USAMRDC: $67,639 SBIR/STTR: $134,000 **Management Costs** $45,856 1.21%	**Research** Consortium Award: $3,752,504
	Total: $4M	**Total: $247,495**	**Total: $3,752,504**

The following abbreviations are used for withholds:
USAMRDC: US Army Medical Research and Development Command
SBIR/STTR: Small Business Innovation Research/Small Business Technology Transfer
Percent of management costs=management costs/(appropriation-withholds)

Table B-2. FY19-FY20 Amyotrophic Lateral Sclerosis Research Program Congressional Language and Appropriations, Withholds and Management Costs, and Execution of Investment Strategy

Fiscal Year	Congressional Language and Appropriations	Withholds and Management Costs	Investment Strategy
2019	**$10M** for Amyotrophic Lateral Sclerosis Research	**Withholds** USAMRDC: $169,110 SBIR/STTR: $335,000 **Management Costs** $290,650 3.06%	**Research** Therapeutic Development Award: $2,803,737 Therapeutic Idea Award: $6,401,503
	Total: $10M	**Total: $794,760**	**Total: $9,205,240**
2020	**$20M** for Amyotrophic Lateral Sclerosis Research	**Withholds** USAMRDC: $386,580 SBIR/STTR: $671,000 **Budgeted Management Costs** $1,292,420 7%	**Research** Budgeted Peer-Reviewed Research: $17,650,000
	Total: $20M	**Total: $2,350,000**	**Total: $17,650,000**

The following abbreviations are used for withholds:
USAMRDC: US Army Medical Research and Development Command
SBIR/STTR: Small Business Innovation Research/Small Business Technology Transfer
Percent of management costs=management costs/(appropriation-withholds)

Table B-3. FY19-FY20 Autism Research Program Congressional Language and Appropriations, Withholds and Management Costs, and Execution of Investment Strategy

Fiscal Year	Congressional Language and Appropriations	Withholds and Management Costs	Investment Strategy
2019	**$7.5M** for Autism Research	**Withholds** USAMRDC: $124,229 SBIR/STTR: $252,000 **Management Costs** $429,661 6.03%	**Research** Clinical Translational Research Award: $1,418,768 Clinical Trial Award: $3,143,927 Idea Development Award: $2,131,415
	Total: $7.5M	**Total: $805,890**	**Total: $6,694,110**
2020	**$15M** for Autism Research	**Withholds** USAMRDC: $289,940 SBIR/STTR: $503,000 **Budgeted Management Costs** $994,000 7%	**Research** Budgeted Peer-Reviewed Research: $13,213,060
	Total: $15M	**Total: $1,786,940**	**Total: $13,213,060**

The following abbreviations are used for withholds:
USAMRDC: US Army Medical Research and Development Command
SBIR/STTR: Small Business Innovation Research/Small Business Technology Transfer
Percent of management costs=management costs/(appropriation-withholds)

Table B-4. FY19-FY20 Bone Marrow Failure Research Program Congressional Language and Appropriations, Withholds and Management Costs, and Execution of Investment Strategy

Fiscal Year	Congressional Language and Appropriations	Withholds and Management Costs	Investment Strategy
2019	**$3M** for Bone Marrow Failure Research	**Withholds** USAMRDC: $50,457 SBIR/STTR: $101,000 **Management Costs** $133,085 4.67%	**Research** Idea Development Award: $2,394,068 Idea Development Award - Established Investigator: 321,390
	Total: $3M	**Total: $284,542**	**Total: $2,715,458**
2020	**$3M** for Bone Marrow Failure Research	**Withholds** USAMRDC: $58,000 SBIR/STTR: $100,000 **Budgeted Management Costs** $198,000 7%	**Research** Budgeted Peer-Reviewed Research: $2,644,000
	Total: $3M	**Total: $356,000**	**Total: $2,644,000**

The following abbreviations are used for withholds:
USAMRDC: US Army Medical Research and Development Command
SBIR/STTR: Small Business Innovation Research/Small Business Technology Transfer
Percent of management costs=management costs/(appropriation-withholds)

Table B-5. FY19-FY20 Breast Cancer Research Program Congressional Language and Appropriations, Withholds and Management Costs, and Execution of Investment Strategy

Fiscal Year	Congressional Language and Appropriations	Withholds and Management Costs	Investment Strategy
2019	**$130M** for Breast Cancer Research **$621,219** proceeds from the Stamp Out Breast Cancer Act	**Withholds** USAMRDC: $2,197,643 SBIR/STTR: $4,361,000 **Management Costs** $7,632,131 6.15%	**Research** Breakthrough Award - Funding Level 1: $10,409,556 Breakthrough Award - Funding Level 1 - Partnering PI Option: $9,387,062 Breakthrough Award - Funding Level 2: $23,203,044 Breakthrough Award - Funding Level 2 - Partnering PI Option: $26,735,294 Breakthrough Award - Funding Level 2 - Population Science and Prevention Studies: $2,395,968 Breakthrough Award - Funding Level 2 - Population Science and Prevention Studies - Partnering PI Option: $3,112,965 Breakthrough Award - Funding Level 3: $4,825,208 Breakthrough Award - Funding Level 3 - Partnering PI Option: $10,592,756 Breakthrough Award - Funding Level 4 - Clinical Trial - Partnering PI Option: $5,486,597 Breakthrough Award - Funding Level 4 - Partnering PI Option Breakthrough Fellowship Award: $1,897,405 Era of Hope Scholar Award: $9,967,375 Expansion Award: $8,417,216
	Total: $130,621,219	**Total: $14,190,774**	**Total: $116,430,446**
2020	**$150M** for Breast Cancer Research **$454,128** proceeds from the Stamp Out Breast Cancer Act	**Withholds** USAMRDC: $2,899,380 SBIR/STTR: $5,031,000 **Budgeted Management Costs** $9,900,000 7%	**Research** Budgeted Peer-Reviewed Research: $132,623,748
	Total: $150,454,128	**Total: $17,830,380**	**Total: $132,623,748**

The following abbreviations are used for withholds:
USAMRDC: US Army Medical Research and Development Command
SBIR/STTR: Small Business Innovation Research/Small Business Technology Transfer
Percent of management costs=management costs/(appropriation-withholds)

Table B-6. FY19-FY20 Chronic Pain Research Program Congressional Language and Appropriations, Withholds and Management Costs, and Execution of Investment Strategy

Fiscal Year	Congressional Language and Appropriations	Withholds and Management Costs	Investment Strategy
2019	**$10M** for Chronic Pain Research	**Withholds** USAMRDC: $168,977 SBIR/STTR: $335,000 **Budgeted Management Costs** $1,081,419 11.39%	**Research** Investigator-Initiated Research Award: $6,887,095 Translational Research Award - Clinical Trial: $1,527,509
	Total: $10M	**Total: $1,585,396**	**Total: $8,414,604**
2020	**$15M** for Chronic Pain Research	**Withholds** USAMRDC: $289,940 SBIR/STTR: $503,000 **Budgeted Management Costs** $994,000 7%	**Research** Budgeted Peer-Reviewed Research: $13,213,060
	Total: $15M	**Total: $1,786,940**	**Total: $13,213,060**

The following abbreviations are used for withholds:
USAMRDC: US Army Medical Research and Development Command
SBIR/STTR: Small Business Innovation Research/Small Business Technology Transfer
Percent of management costs=management costs/(appropriation-withholds)

Table B-7. FY19-FY20 Combat Readiness Research Program Congressional Language and Appropriations, Withholds and Management Costs, and Execution of Investment Strategy

Fiscal Year	Congressional Language and Appropriations	Withholds and Management Costs	Investment Strategy
2019	**$15M** for Combat Readiness Research	**Withholds** USAMRDC: $253,960 SBIR/STTR: $488,000 **Budgeted Management Costs** $1,119,910 7.85%	**Research** Rapid Development and Translational Research Award: $13,138,130
	Total: $15M	**Total: $1,861,870**	**Total: $13,138,130**
2020	**$10M** for Combat Readiness Research	**Withholds** USAMRDC: $193,300 SBIR/STTR: $335,000 **Budgeted Management Costs** $663,000 7%	**Research** Budgeted Peer-Reviewed Research: $8,808,700
	Total: $10M	**Total: $1,191,300**	**Total: $8,808,700**

The following abbreviations are used for withholds:
USAMRDC: US Army Medical Research and Development Command
SBIR/STTR: Small Business Innovation Research/Small Business Technology Transfer
Percent of management costs=management costs/(appropriation-withholds)

Table B-8. FY19-FY20 Duchenne Muscular Dystrophy Research Program Congressional Language and Appropriations, Withholds and Management Costs, and Execution of Investment Strategy

Fiscal Year	Congressional Language and Appropriations	Withholds and Management Costs	Investment Strategy
2019	**$3.2M** for Duchenne Muscular Dystrophy Research	**Withholds** USAMRDC: $51,968 SBIR/STTR: $107,000 **Management Costs** $157,581 5.18%	**Research** Idea Development Award: $2,740,780 Investigator-Initiated Research Award - Optional Multidiscipline Collaborator: $142,671
	Total: $3.2M	**Total: $316,549**	**Total: $2,883,451**
2020	**$10M** for Duchenne Muscular Dystrophy Research	**Withholds** USAMRDC: $193,300 SBIR/STTR: $335,000 **Budgeted Management Costs** $663,000 7%	**Budgeted Research** Budgeted Peer-Reviewed Research: $8,808,700
	Total: $10M	**Total: $1,191,300**	**Total: $8,808,700**

The following abbreviations are used for withholds:
USAMRDC: US Army Medical Research and Development Command
SBIR/STTR: Small Business Innovation Research/Small Business Technology Transfer
Percent of management costs=management costs/(appropriation-withholds)

Table B-9. FY19-FY20 Epilepsy Research Program Congressional Language and Appropriations, Withholds and Management Costs, and Execution of Investment Strategy

Fiscal Year	Congressional Language and Appropriations	Withholds and Management Costs	Investment Strategy
2019	**$7.5M** for Epilepsy Research	**Withholds** USAMRDC: $124,167 SBIR/STTR: $252,000 **Management Costs** $343,919 4.83%	**Research** Epilepsy Risk Factors Award: $18,945 Idea Development Award - Funding Level 1: $457,454 Idea Development Award - Funding Level 2: $3,035,692 Research Partnership Award - Funding Level 1: $1,299,973 Research Partnership Award - Funding Level 2: $1,967,850
	Total: $7.5M	**Total: $720,086**	**Total: $6,779,914**
2020	**$12M** for Epilepsy Research	**Withholds** USAMRDC: $231,940 SBIR/STTR: $403,000 **Budgeted Management Costs** $750,000 7%	**Research** Budgeted Peer-Reviewed Research: $10,615,060
	Total: $12M	**Total: $1,384,940**	**Total: $10,615,060**

The following abbreviations are used for withholds:
USAMRDC: US Army Medical Research and Development Command
SBIR/STTR: Small Business Innovation Research/Small Business Technology Transfer
Percent of management costs=management costs/(appropriation-withholds)

Table B-10. FY19-FY20 Gulf War Illness Research Program Congressional Language and Appropriations, Withholds and Management Costs, and Execution of Investment Strategy

Fiscal Year	Congressional Language and Appropriations	Withholds and Management Costs	Investment Strategy
2019	**$22M** for Gulf War Illness Research	**Withholds** USAMRDC: $366,911 SBIR/STTR: $705,000 **Management Costs** $1,223,089 5.84%	**Research** Clinical Consortium Award: $925,933 Clinical Evaluation Award: $1,626,379 Gulf War Illness Epidemiology Research Award: $447,910 Idea Award: $209,251 Investigator-Initiated Focused Research Award - Tier 1: $5,175 Investigator-Initiated Focused Research Award - Tier 2: $99,634 New Investigator Award: $2,199,846 Patient-Provider and Health Communications Award: $857,803 Research Advancement Award: $5,436,456 Therapeutic/Biomarker Trial Award: $7,896,613
	Total: $22M	**Total: $2,295,000**	**Total: $19,705,000**
2020	**$22M** for Gulf War Illness Research	**Withholds** USAMRDC: $425,860 SBIR/STTR: $707,000 **Budgeted Management Costs** $1,457,000 7%	**Research** Budgeted Peer-Reviewed Research: $19,410,140
	Total: $22M	**Total: $2,589,860**	**Total: $19,410,140**

The following abbreviations are used for withholds:
USAMRDC: US Army Medical Research and Development Command
SBIR/STTR: Small Business Innovation Research/Small Business Technology Transfer
Percent of management costs=management costs/(appropriation-withholds)

Table B-11. FY19-FY20 Hearing Restoration Research Program Congressional Language and Appropriations, Withholds and Management Costs, and Execution of Investment Strategy

Fiscal Year	Congressional Language and Appropriations	Withholds and Management Costs	Investment Strategy
2019	**$10M** for Hearing Restoration Research	**Withholds** USAMRDC: $169,138 SBIR/STTR: $335,000 **Budgeted Management Costs** $613,432 6.46%	**Research** Focused Applied Research Award: $282,356 Focused Research Award - Funding Level 1: $2,148,724 Focused Research Award - Funding Level 2: $4,479,130 Focused Research Award - Funding Level 2 with Pilot Clinical Trial Option: $1,972,220
	Total: $10M	**Total: $1,117,570**	**Total: $8,882,430**
2020	**$10M** for Hearing Restoration Research	**Withholds** USAMRDC: $193,300 SBIR/STTR: $335,000 **Budgeted Management Costs** $663,000 7%	**Research** Budgeted Peer-Reviewed Research: $8,808,700
	Total: $10M	**Total: $1,191,300**	**Total: $8,808,700**

The following abbreviations are used for withholds:
USAMRDC: US Army Medical Research and Development Command
SBIR/STTR: Small Business Innovation Research/Small Business Technology Transfer
Percent of management costs=management costs/(appropriation-withholds)

Table B-12. FY19-FY20 Joint Warfighter Medical Research Program Congressional Language and Appropriations, Withholds and Management Costs, and Execution of Investment Strategy

Fiscal Year	Congressional Language and Appropriations	Withholds and Management Costs	Investment Strategy
2019	**$50M** for Joint Warfighter Medical Research	**Withholds** USAMRDC: $810,302 SBIR/STTR: $1,626,000 **Budgeted Management Costs** $1,572,281 3.31%	**Budgeted Research** Peer-Reviewed Research: $45,991,417
	Total: $50M	**Total: $4,008,583**	**Total: $45,991,417**
2020	**$40M** for Joint Warfighter Medical Research	**Withholds** USAMRDC: $773,400 SBIR/STTR: $1,330,000 **Budgeted Management Costs** $2,630,000 7%	**Budgeted Research** Budgeted Peer-Reviewed Research: $35,266,600
	Total: $40M	**Total: $4,733,400**	**Total: $35,266,600**

The following abbreviations are used for withholds:
USAMRDC: US Army Medical Research and Development Command
SBIR/STTR: Small Business Innovation Research/Small Business Technology Transfer
Percent of management costs=management costs/(appropriation-withholds)

Table B-13. FY19-FY20 Kidney Cancer Research Program Congressional Language and Appropriations, Withholds and Management Costs, and Execution of Investment Strategy

Fiscal Year	Congressional Language and Appropriations	Withholds and Management Costs	Investment Strategy
2019	**$20M** for Kidney Cancer Research	**Withholds** USAMRDC: $336,865 SBIR/STTR: $686,000 **Budgeted Management Costs** $678,990 3.58%	**Research** Clinical Consortium Award: $2,395,957 Concept Award: $700,525 Idea Development Award: $8,029,714 Kidney Cancer Academy - Dean Award: $716,990 Kidney Cancer Academy - Early-Career Investigator Award: $3,547,214 Translational Research Partnership Award: $2,907,745
	Total: $20M	**Total: $1,701,855**	**Total: $18,298,145**
2020	**$40M** for Kidney Cancer Research	**Withholds** USAMRDC: $773,180 SBIR/STTR: $1,341,000 **Budgeted Management Costs** $2,650,000 7%	**Research** Budgeted Peer-Reviewed Research: $35,235,820
	Total: $40M	**Total: $4,764,180**	**Total: $35,235,820**

The following abbreviations are used for withholds:
USAMRDC: US Army Medical Research and Development Command
SBIR/STTR: Small Business Innovation Research/Small Business Technology Transfer
Percent of management costs=management costs/(appropriation-withholds)

Table B-14. FY19-FY20 Lung Cancer Research Program Congressional Language and Appropriations, Withholds and Management Costs, and Execution of Investment Strategy

Fiscal Year	Congressional Language and Appropriations	Withholds and Management Costs	Investment Strategy
2019	**$14M** for Lung Cancer Research	**Withholds** USAMRDC: $232,040 SBIR/STTR: $470,000 **Management Costs** $1,441,458 10.84%	**Research** Career Development Award: $1,985,794 Concept Award: $2,041,120 Idea Development Award - Established Investigator: $1,026,650 Idea Development Award - New Investigator: $2,913,355 Investigator-Initiated Translational Research Award: $1,331,816 Translational Research Partnership Award: $1,171,766 Translational Research Partnership Award - Clinical Trial: $1,386,001
	Total: $14M	**Total: $2,143,498**	**Total: $11,856,502**
2020	**$14M** for Lung Cancer Research	**Withholds** USAMRDC: $270,600 SBIR/STTR: $470,000 **Budgeted Management Costs** $927,000 7%	**Research** Budgeted Peer-Reviewed Research: $12,332,400
	Total: $14M	**Total: $1,667,600**	**Total: $12,332,400**

The following abbreviations are used for withholds:
USAMRDC: US Army Medical Research and Development Command
SBIR/STTR: Small Business Innovation Research/Small Business Technology Transfer
Percent of management costs=management costs/(appropriation-withholds)

Table B-15. FY19-FY20 Lupus Research Program Congressional Language and Appropriations, Withholds and Management Costs, and Execution of Investment Strategy

Fiscal Year	Congressional Language and Appropriations	Withholds and Management Costs	Investment Strategy
2019	**$5M** for Lupus Research	**Withholds** USAMRDC: $82,911 SBIR/STTR: $168,000 **Budgeted Management Costs** $284,758 6.00%	**Research** Concept Award: $1,392,558 Impact Award: $3,071,773
	Total: $5M	**Total: $535,669**	**Total: $4,464,331**
2020	**$10M** for Lupus Research	**Withholds** USAMRDC: $193,300 SBIR/STTR: $335,000 **Budgeted Management Costs** $663,000 7%	**Research** Budgeted Peer-Reviewed Research: $8,808,700
	Total: $10M	**Total: $1,191,300**	**Total: $8,808,700**

The following abbreviations are used for withholds:
USAMRDC: US Army Medical Research and Development Command
SBIR/STTR: Small Business Innovation Research/Small Business Technology Transfer
Percent of management costs=management costs/(appropriation-withholds)

Table B-16. FY19-FY20 Melanoma Research Program Congressional Language and Appropriations, Withholds and Management Costs, and Execution of Investment Strategy

Fiscal Year	Congressional Language and Appropriations	Withholds and Management Costs	Investment Strategy
2019	**$10M** for Melanoma Research	**Withholds** USAMRDC: $160,878 SBIR/STTR: $335,000 **Budgeted Management Costs** $845,123 8.89%	**Research** Concept Award: $492,429 Idea Award: $3,476,427 Team Science Award: $1,818,345 Translational Research Award: $2,871,798
	Total: $10M	**Total: $1,341,001**	**Total: $8,658,999**
2020	**$20M** for Melanoma Research	**Withholds** USAMRDC: $386,580 SBIR/STTR: $671,000 **Budgeted Management Costs** $1,300,000 7%	**Research** Budgeted Peer-Reviewed Research: $17,642,420
	Total: $20M	**Total: $2,357,580**	**Total: $17,642,420**

The following abbreviations are used for withholds:
USAMRDC: US Army Medical Research and Development Command
SBIR/STTR: Small Business Innovation Research/Small Business Technology Transfer
Percent of management costs=management costs/(appropriation-withholds)

Table B-17. FY19-FY20 Military Burn Research Program Congressional Language and Appropriations, Withholds and Management Costs, and Execution of Investment Strategy

Fiscal Year	Congressional Language and Appropriations	Withholds and Management Costs	Investment Strategy
2019	**$8M** for Military Burn Research	**Withholds** USAMRDC: $139,386 **Budgeted Management Costs** $222,035 2.82%	**Research** Clinical Translational Research Award - Clinical Trial: $2,982,698 Clinical Trial Award - Research Level 2: $318,706 Idea Development Award: $4,337,175
	Total: $8M	**Total: $361,421**	**Total: $7,638,579**
2020	**$10M** for Military Burn Research	**Withholds** USAMRDC: $200,000 **Budgeted Management Costs** $663,000 7%	**Research** Budgeted Peer-Reviewed Research: $9,137,000
	Total: $10M	**Total: $863,000**	**Total: $9,137,000**

The following abbreviations are used for withholds:
USAMRDC: US Army Medical Research and Development Command
SBIR/STTR: Small Business Innovation Research/Small Business Technology Transfer
Percent of management costs=management costs/(appropriation-withholds)

Table B-18. FY19-FY20 Multiple Sclerosis Research Program Congressional Language and Appropriations, Withholds and Management Costs, and Execution of Investment Strategy

Fiscal Year	Congressional Language and Appropriations	Withholds and Management Costs	Investment Strategy
2019	**$6M** for Multiple Sclerosis Research	**Withholds** USAMRDC: $99,096 SBIR/STTR: $201,000 **Management Costs** $594,081 10.42%	**Research** Exploration - Hypothesis Development Award: $1,472,451 Investigator-Initiated Research Award: $3,633,372
	Total: $6M	**Total: $894,177**	**Total: $5,105,823**
2020	**$16M** for Multiple Sclerosis Research	**Withholds** USAMRDC: $309,260 SBIR/STTR: $537,000 **Budgeted Management Costs** $1,060,000 7%	**Research** Budgeted Peer-Reviewed Research: $14,093,740
	Total: $16M	**Total: $1,906,260**	**Total: $14,093,740**

The following abbreviations are used for withholds:
USAMRDC: US Army Medical Research and Development Command
SBIR/STTR: Small Business Innovation Research/Small Business Technology Transfer
Percent of management costs=management costs/(appropriation-withholds)

Table B-19. FY19-FY20 Neurofibromatosis Research Program Congressional Language and Appropriations, Withholds and Management Costs, and Execution of Investment Strategy

Fiscal Year	Congressional Language and Appropriations	Withholds and Management Costs	Investment Strategy
2019	**$15M** for Neurofibromatosis Research	**Withholds** USAMRDC: $261,729 **Management Costs** $619,211 4.20%	**Research** Clinical Trial Award: $1,749,458 Early Investigator Research Award: $1,168,800 Exploration - Hypothesis Development Award: $303,945 Investigator-Initiated Research Award: $5,747,080 New Investigator Award: $5,149,777
	Total: $15M	**Total: $880,940**	**Total: $14,119,060**
2020	**$15M** for Neurofibromatosis Research	**Withholds** USAMRDC: $300,000 **Budgeted Management Costs** $1,000,000 7%	**Research** Budgeted Peer-Reviewed Research: $13,700,000
	Total: $15M	**Total: $1,300,000**	**Total: $13,700,000**

The following abbreviations are used for withholds:
USAMRDC: US Army Medical Research and Development Command
SBIR/STTR: Small Business Innovation Research/Small Business Technology Transfer
Percent of management costs=management costs/(appropriation-withholds)

Table B-20. FY19-FY20 Orthotics and Prosthetics Outcomes Research Program Congressional Language and Appropriations, Withholds and Management Costs, and Execution of Investment Strategy

Fiscal Year	Congressional Language and Appropriations	Withholds and Management Costs	Investment Strategy
2019	**$10M** for Orthotics and Prosthetics Outcomes Research	**Withholds** USAMRDC: $166,414 SBIR/STTR: $335,000 **Management Costs** $453,507 4.77%	**Research** Clinical Research Award - Funding Level 1: $1,698,320 Clinical Research Award - Funding Level 2: $999,767 Clinical Trial Award - Funding Level 2: $5,999,869 Clinical Trial Award - Funding Level 1: $347,123
	Total: $10M	**Total: $954,921**	**Total: $9,045,079**
2020	**$15M** for Orthotics and Prosthetics Outcomes Research	**Withholds** USAMRDC: $289,940 SBIR/STTR: $503,000 **Budgeted Management Costs** $990,000 7%	**Research** Budgeted Peer-Reviewed Research: $13,217,060
	Total: $15M	**Total: $1,782,940**	**Total: $13,217,060**

The following abbreviations are used for withholds:
USAMRDC: US Army Medical Research and Development Command
SBIR/STTR: Small Business Innovation Research/Small Business Technology Transfer
Percent of management costs=management costs/(appropriation-withholds)

Table B-21. FY19-FY20 Ovarian Cancer Research Program Congressional Language and Appropriations, Withholds and Management Costs, and Execution of Investment Strategy

Fiscal Year	Congressional Language and Appropriations	Withholds and Management Costs	Investment Strategy
2019	**$20M** for Ovarian Cancer Research	**Withholds** USAMRDC: $336,730 SBIR/STTR: $671,000 **Management Costs** $1,079,720 5.69%	**Research** Clinical Development Award - Clinical Trial: $909,279 Clinical Development Award - Optional Nested Early Career Investigator - Clinical Trial: $1,120,216 Investigator-Initiated Research Award: $6,442,238 Outcomes Consortium Award: $520,259 Ovarian Cancer Academy - Early-Career Investigator Award: $2,178,866 Ovarian Cancer Academy Dean and Assistant Dean (Leadership) Award: $2,839,375 Pilot Award: $3,902,317
	Total: $20M	**Total: $2,087,450**	**Total: $17,912,550**
2020	**$35M** for Ovarian Cancer Research	**Withholds** USAMRDC: $676,520 SBIR/STTR: $1,174,000 **Budgeted Management Costs** $2,300,000 7%	**Research** Budgeted Peer-Reviewed Research: $30,849,480
	Total: $35M	**Total: $4,150,520**	**Total: $30,849,480**

The following abbreviations are used for withholds:
USAMRDC: US Army Medical Research and Development Command
SBIR/STTR: Small Business Innovation Research/Small Business Technology Transfer
Percent of management costs=management costs/(appropriation-withholds)

Table B-22. FY19-FY20 Neurotoxin Exposure Treatment Program Congressional Language and Appropriations, Withholds and Management Costs, and Execution of Investment Strategy

Fiscal Year	Congressional Language and Appropriations	Withholds and Management Costs	Investment Strategy
2019	**$16M** for Neurotoxin Exposure Treatment Program	**Withholds** USAMRDC: $276,492 **Management Costs** $945,489 6.01%	**Research** Early Investigator Research Award: $1,797,860 Investigator-Initiated Research Award: $5,877,227 Investigator-Initiated Research Award: Partnering PI Option: $7,102,932
	Total: $16M	**Total: $1,221,981**	**Total: $14,778,019**
2020	**$16M** for Neurotoxin Exposure Treatment Program	**Withholds** USAMRDC: $320,000 **Budgeted Management Costs** $1,070,000 7%	**Research** Budgeted Peer-Reviewed Research: $14,610,000
	Total: $16M	**Total: $1,390,000**	**Total: $14,610,000**

The following abbreviations are used for withholds:
USAMRDC: US Army Medical Research and Development Command
SBIR/STTR: Small Business Innovation Research/Small Business Technology Transfer
Percent of management costs=management costs/(appropriation-withholds)

Table B-23. FY19-FY20 Peer Reviewed Alzheimer's Research Program Congressional Language and Appropriations, Withholds and Management Costs, and Execution of Investment Strategy

Fiscal Year	Congressional Language and Appropriations	Withholds and Management Costs	Investment Strategy
2019	**$15M** for Peer Reviewed Alzheimer's Research	**Withholds** USAMRDC: $253,285 SBIR/STTR: $503,000 **Management Costs** $816,915 5.74%	**Research** Convergence Science Research Awards - Funding Level 1: $925,634 Convergence Science Research Awards - Funding Level 2: $3,788,341 Innovations in Care and Support Award - Funding Level 1: $354,188 Innovations in Care and Support Awards - Funding Level 2: $1,766,400 Research Partnership Award: $6,592,237
	Total: $15M	**Total: $1,573,200**	**Total: $13,426,800**
2020	**$15M** for Peer Reviewed Alzheimer's Research	**Withholds** USAMRDC: $289,940 SBIR/STTR: $503,000 **Budgeted Management Costs** $990,000 7%	**Research** Budgeted Peer-Reviewed Research: $13,217,060
	Total: $15M	**Total: $1,782,940**	**Total: $13,217,060**

The following abbreviations are used for withholds:
USAMRDC: US Army Medical Research and Development Command
SBIR/STTR: Small Business Innovation Research/Small Business Technology Transfer
Percent of management costs=management costs/(appropriation-withholds)

Table B-24. FY19-FY20 Peer Reviewed Cancer Research Program Congressional Language and Appropriations, Withholds and Management Costs, and Execution of Investment Strategy

Fiscal Year	Congressional Language and Appropriations	Withholds and Management Costs	Investment Strategy
2019	**$90M** for Peer-Reviewed Cancer Research	**Withholds** USAMRDC: $1,391,753 SBIR/STTR: $3,049,000 **Management Costs** $5,288,243 6.18%	**Research** Bladder Cancer: $6,437,845 Blood Cancers: $8,178,698 Brain Cancer: $5,647,383 Cancer in Children, Adolescents, and Young Adults: $7,425,160 Colorectal Cancer: $8,435,727 Immunotherapy: $7,580,845 Liver Cancer: $7,049,895 Lymphoma: $1,586,138 Mesothelioma: $5,632,698 Neuroblastoma: $4,907,579 Pancreatic Cancer: $5,069,558 Pediatric Brain Tumors: $3,234,982 Rare Cancers: $4,711,460 Stomach Cancer: $4,373,036
	Total: $90M	**Total: $9,728,996**	**Total: 80,271,004**
2020	**$110M** for Peer-Reviewed Cancer Research	**Withholds** USAMRDC: $2,126,200 SBIR/STTR: $3,690,000 **Budgeted Management Costs** $7,200,000 7%	**Research** Budgeted Peer-Reviewed Research: $96,983,800
	Total: $110M	**Total: $13,016,200**	**Total: $96,983,800**

The following abbreviations are used for withholds:
USAMRDC: US Army Medical Research and Development Command
SBIR/STTR: Small Business Innovation Research/Small Business Technology Transfer
Percent of management costs=management costs/(appropriation-withholds)
FY20 Peer Reviewed Cancer Research Program: The agreement provides $110,000,000 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, esophageal cancer, head and neck cancer, immunotherapy, liver cancer, mesothelioma, metastatic cancer, neuroblastoma, pediatric brain tumors, pediatric, adolescent, and young adult cancers, stomach cancer.

Table B-25. FY19-FY20 Peer Reviewed Medical Research Program Congressional Language and Appropriations, Withholds and Management Costs, and Execution of Investment Strategy

Fiscal Year	Congressional Language and Appropriations	Withholds and Management Costs	Investment Strategy
2019	**$350M** for Peer-Reviewed Medical Research	**Withholds** USAMRDC: $5,704,576 SBIR/STTR: $11,691,000 **Management Costs** $15,925,778 4.79%	**Research** Acute Lung Injury: $23,451,829 Antimicrobial Resistance: $14,706,695 Arthritis: $1,200,000 Cardiomyopathy: $26,388,787 Congenital Heart Disease: $23,272,257 Diabetes: $36,988,185 Dystonia: $723,999 Eating Disorders: $314,634 Emerging Infectious Diseases: $13,464,090 Focal Segmental Glomerulo-sclerosis: $6,571,654 Frontotemporal Degeneration: $4,949,630 Guillain-Barré Syndrome: $1,593,787 Hemorrhage Control: $17,527,630 Hepatitis B: $4,444,470 Hydrocephalus: $2,303,207 Immunomonitoring of Intestinal Transplants: $324,000 Inflammatory Bowel Diseases: $7,733,014 Lung Injury: $708,523 Mitochondrial Disease: $14,730,669 Musculoskeletal Disorders: $12,745,416 Myotonic Dystrophy: $2,368,891 Nanomaterials for Bone Regeneration: $6,192,445 Nutrition Optimization: $1,970,551 Pancreatitis: $4,298,631 Polycystic Kidney Disease: $8,368,938 Post-Traumatic Osteoarthritis: $9,519,040 Pulmonary Fibrosis: $17,847,765 Resilience Training: $348,086 Respiratory Health: $18,768,541 Rett Syndrome: $1,526,748 Rheumatoid Arthritis: $6,289,457 Scleroderma: $2,557,203 Sleep Disorders: $5,144,585 Spinal Muscular Atrophy: $0 Tissue Regeneration: $10,900,527 Tuberculosis: $5,825,231 Women's Heart Disease: $609,531
	Total: $350M	**Total: $33,321,354**	**Total: $316,678,646**
2020	**$360M** for Peer-Reviewed Medical Research	**Withholds** USAMRDC: $6,966,100 SBIR/STTR: $11,695,000 **Budgeted Management Costs** $17,300,000 5%	**Research** Budgeted Peer-Reviewed Research: $324,038,900
	Total: $360M	**Total: $35,961,100**	**Total: $324,038,900**

The following abbreviations are used for withholds:
USAMRDC: US Army Medical Research and Development Command
SBIR/STTR: Small Business Innovation Research/Small Business Technology Transfer
Percent of management costs=management costs/(appropriation-withholds)
FY20 Peer Reviewed Medical Research Program: The agreement provides $360,000,000 for a peer-reviewed medical research program. The Secretary of Defense, in conjunction with the Service Surgeons General, is directed to select medical research projects of clear scientific merit and direct relevance to military health. Research areas considered under this funding are restricted to the following areas: arthritis, burn pit exposure, chronic migraine and post-traumatic headache, congenital heart disease, constrictive bronchiolitis, diabetes, dystonia, eating disorders, emerging viral diseases, endometriosis, epidermolusis bullosa, familial hypercholesterolemia, fibrous dysplasia, focal segmental glomerulosclerosis, food allergies, Fragile X syndrome, frontotemporal degeneration, Guillain-Barre syndrome, hemorrhage control, hepatitis B, hydrocephalus, immunomonitoring of intestinal transplants, inflammatory bowel disease, interstitial cystitis, metals toxicology, mitochondrial disease, musculoskeletal health, myalgic encephalomyelitis/chronic fatigue syndrome, myotonic dystrophy, nutrition optimization, pancreatitis, pathogen-inactivated blood products, plant-based vaccines, polycystic kidney disease, pressure ulcers, pulmonary fibrosis, resilience training, respiratory health, rheumatoid arthritis, sleep disorders and restriction, spinal muscular atrophy, sustained-release drug delivery, vascular malformations, and women's heart disease.

Table B-26. FY19-FY20 Peer Reviewed Orthopaedic Research Program Congressional Language and Appropriations, Withholds and Management Costs, and Execution of Investment Strategy

Fiscal Year	Congressional Language and Appropriations	Withholds and Management Costs	Investment Strategy
2019	**$30M** for Peer-Reviewed Orthopedic Research	**Withholds** USAMRDC: $507,395 SBIR/STTR: $1,006,000 **Management Costs** $1,995,439 7.00%	**Research** Applied Research Award: $9,795,640 Clinical Translational Research Award: $6,522,562 Clinical Trial Award: $1,333,494 Clinical Trial Award - Funding Level 1: $5,855,607 Clinical Trial Award - Funding Level 2: $2,839,078 Outcomes Research Award: $144,785
	Total: $30M	**Total: $3,508,834**	**Total: $26,491,166**
2020	**$30M** for Peer-Reviewed Orthopedic Research	**Withholds** USAMRDC: $579,880 SBIR/STTR: $1,006,000 **Budgeted Management Costs** $1,900,000 7%	**Research** Budgeted Peer-Reviewed Research: $26,514,120
	Total: $30M	**Total: $3,485,880**	**Total: $26,514,120**

The following abbreviations are used for withholds:
USAMRDC: US Army Medical Research and Development Command
SBIR/STTR: Small Business Innovation Research/Small Business Technology Transfer
Percent of management costs=management costs/(appropriation-withholds)

Table B-27. FY20 Peer Reviewed Pancreatic Research Program Congressional Language and Appropriations, Withholds and Management Costs, and Execution of Investment Strategy

Fiscal Year	Congressional Language and Appropriations	Withholds and Management Costs	Investment Strategy
2020	**$6M** for Peer-Reviewed Pancreatic Research	**Withholds** USAMRDC: $115,980 SBIR/STTR: $201,000 **Budgeted Management Costs** $390,000 7%	**Research** Budgeted Peer-Reviewed Research: $5,293,020
	Total: $6M	**Total: $706,980**	**Total: $5,293,020**

The following abbreviations are used for withholds:
USAMRDC: US Army Medical Research and Development Command
SBIR/STTR: Small Business Innovation Research/Small Business Technology Transfer
Percent of management costs=management costs/(appropriation-withholds)

Table B-28. FY20 Peer Reviewed Rare Cancers Research Program Congressional Language and Appropriations, Withholds and Management Costs, and Execution of Investment Strategy

Fiscal Year	Congressional Language and Appropriations	Withholds and Management Costs	Investment Strategy
2020	**$7.5M** for Peer-Reviewed Rare Cancers Research	**Withholds** USAMRDC: $144,960 SBIR/STTR: $252,000 **Budgeted Management Costs** $490,000 7%	**Research** Budgeted Peer-Reviewed Research: $6,613,040
	Total: $7.5M	**Total: $886,960**	**Total: $6,613,040**

The following abbreviations are used for withholds:
USAMRDC: US Army Medical Research and Development Command
SBIR/STTR: Small Business Innovation Research/Small Business Technology Transfer
Percent of management costs=management costs/(appropriation-withholds)

Table B-29. FY19-FY20 Prostate Cancer Research Program Congressional Language and Appropriations, Withholds and Management Costs, and Execution of Investment Strategy

Fiscal Year	Congressional Language and Appropriations	Withholds and Management Costs	Investment Strategy
2019	**$100M** for Prostate Cancer Research	**Withholds** USAMRDC: $1,690,678 SBIR/STTR: $3,355,000 **Management Costs** $5,262,793 5.54%	**Research** Clinical Consortium Award - Clinical Research Site: $276,447 Clinical Consortium Research Site Award: $306,000 Clinical Trial Award: $10,881,566 Early Investigator Research Award: $6,040,185 Health Disparity Research Award - Established Investigator: $6,412,568 Health Disparity Research Award - New Investigator: $3,745,887 Idea Development Award - Established Investigator: $32,665,929 Idea Development Award - New Investigator: $7,475,352 Idea Expansion Award: $5,308,620 Physician Research Award: $8,286,119 Translational Science Award: $8,292,856
	Total: $100M	**Total: $10,308,471**	**Total: $89,691,529**
2020	**$110M** for Prostate Cancer Research	**Withholds** USAMRDC: $2,126,200 SBIR/STTR: $3,690,000 **Budgeted Management Costs** $7,200,000 7%	**Research** Budgeted Peer-Reviewed Research: $96,983,800
	Total: $110M	**Total: $13,016,200**	**Total: $96,983,800**

The following abbreviations are used for withholds:
USAMRDC: US Army Medical Research and Development Command
SBIR/STTR: Small Business Innovation Research/Small Business Technology Transfer
Percent of management costs=management costs/(appropriation-withholds)

Table B-30. FY19-FY20 Reconstructive Transplant Research Program Congressional Language and Appropriations, Withholds and Management Costs, and Execution of Investment Strategy

Fiscal Year	Congressional Language and Appropriations	Withholds and Management Costs	Investment Strategy
2019	**$12M** for Reconstructive Transplant Research	**Withholds** USAMRDC: $202,843 SBIR/STTR: $403,000 **Management Costs** $581,890 5.11%	**Research** Idea Discovery Award: $1,768,057 Investigator-Initiated Research Award: $6,495,249 Qualitative Research Award: $2,548,961
	Total: $12M	**Total: $1,187,733**	**Total: $10,812,267**
2020	**$12M** for Reconstructive Transplant Research	**Withholds** USAMRDC: $231,940 SBIR/STTR: $403,000 **Budgeted Management Costs** $750,000 7%	**Research** Budgeted Peer-Reviewed Research: $10,615,060
	Total: $12M	**Total: $1,384,940**	**Total: $10,615,060**

The following abbreviations are used for withholds:
USAMRDC: US Army Medical Research and Development Command
SBIR/STTR: Small Business Innovation Research/Small Business Technology Transfer
Percent of management costs=management costs/(appropriation-withholds)

Table B-31. FY20 Scleroderma Research Program Congressional Language and Appropriations, Withholds and Management Costs, and Execution of Investment Strategy

Fiscal Year	Congressional Language and Appropriations	Withholds and Management Costs	Investment Strategy
2020	**$5M** for Scleroderma Research	**Withholds** USAMRDC: $96,640 SBIR/STTR: $168,000 **Budgeted Management Costs** $330,000 7%	**Research** Budgeted Peer-Reviewed Research: $4,405,360
	Total: $5M	**Total: $594,640**	**Total: $4,405,360**

The following abbreviations are used for withholds:
USAMRDC: US Army Medical Research and Development Command
SBIR/STTR: Small Business Innovation Research/Small Business Technology Transfer
Percent of management costs=management costs/(appropriation-withholds)

Table B-32. FY19-FY20 Spinal Cord Injury Research Program Congressional Language and Appropriations, Withholds and Management Costs, and Execution of Investment Strategy

Fiscal Year	Congressional Language and Appropriations	Withholds and Management Costs	Investment Strategy
2019	**$30M** for Spinal Cord Injury Research	**Withholds** USAMRDC: $507,374 SBIR/STTR: $1,006,000 **Management Costs** $2,007,045 7.05%	**Research** Clinical Trial Award: $7,505,813 Expansion Award: $3,811,890 Investigator-Initiated Research Award: $6,465,921 Translational Research Award: $8,695,957
	Total: $30M	**Total: $3,520,419**	**Total: $26,479,581**
2020	**$40M** for Spinal Cord Injury Research	**Withholds** USAMRDC: $773,180 SBIR/STTR: $1,341,000 **Budgeted Management Costs** $2,600,000 7%	**Research** Budgeted Peer-Reviewed Research: $35,285,820
	Total: $40M	**Total: $4,714,180**	**Total: $35,285,820**

The following abbreviations are used for withholds:
USAMRDC: US Army Medical Research and Development Command
SBIR/STTR: Small Business Innovation Research/Small Business Technology Transfer
Percent of management costs=management costs/(appropriation-withholds)

Table B-33. FY19-FY20 Tick-Borne Disease Research Program Congressional Language and Appropriations, Withholds and Management Costs, and Execution of Investment Strategy

Fiscal Year	Congressional Language and Appropriations	Withholds and Management Costs	Investment Strategy
2019	**$5M** for Tick-Borne Disease Research	**Withholds** USAMRDC: $84,442 SBIR/STTR: $168,000 **Management Costs** $270,937 5.71%	**Research** Career Development Award: $753,080 Idea Award: $1,242,895 Investigator-Initiated Research Award: $2,480,646
	Total: $5M	**Total: $523,379**	**Total: $4,476,621**
2020	**$7M** for Tick-Borne Disease Research	**Withholds** USAMRDC: $135,300 SBIR/STTR: $235,000 **Budgeted Management Costs** $460,000 7%	**Research** Budgeted Peer-Reviewed Research: $6,169,700
	Total: $7M	**Total: $830,300**	**Total: $6,169,700**

The following abbreviations are used for withholds:
USAMRDC: US Army Medical Research and Development Command
SBIR/STTR: Small Business Innovation Research/Small Business Technology Transfer
Percent of management costs=management costs/(appropriation-withholds)

Table B-34. FY19-FY20 Tuberous Sclerosis Complex Research Program Congressional Language and Appropriations, Withholds and Management Costs, and Execution of Investment Strategy

Fiscal Year	Congressional Language and Appropriations	Withholds and Management Costs	Investment Strategy
2019	**$6M** for Tuberous Sclerosis Complex Research	**Withholds** USAMRDC: $94,320 SBIR/STTR: $201,000 **Management Costs** $285,354 5.00%	**Research** Clinical Translational Research Award: $1,669,646 Clinical Translational Research Award - Correlative Study: $798,660 Exploration - Hypothesis Development Award: $808,121 Idea Development Award - Established Investigator: $1,474,931 Idea Development Award - New Investigator: $667,968
	Total: $6M	**Total: $580,674**	**Total: $5,419,326**
2020	**$6M** for Tuberous Sclerosis Complex Research	**Withholds** USAMRDC: $115,980 SBIR/STTR: $201,000 **Budgeted Management Costs** $390,000 7%	**Research** Budgeted Peer-Reviewed Research: $5,293,020
	Total: $6M	**Total: $706,980**	**Total: $5,293,020**

The following abbreviations are used for withholds:
USAMRDC: US Army Medical Research and Development Command
SBIR/STTR: Small Business Innovation Research/Small Business Technology Transfer
Percent of management costs=management costs/(appropriation-withholds)

Table B-35. FY19-FY20 Vision Research Program Congressional Language and Appropriations, Withholds and Management Costs, and Execution of Investment Strategy

Fiscal Year	Congressional Language and Appropriations	Withholds and Management Costs	Investment Strategy
2019	**$20M** for Vision Research	**Withholds** USAMRDC: $332,244 SBIR/STTR: $686,000 **Management Costs** $1,182,915 6.23%	**Research** Focused Translational Team Science Award: $4,967,689 Investigator-Initiated Research Award - Funding Level 1: $4,062,018 Investigator-Initiated Research Award - Funding Level 2: $4,492,105 Translational Research Award: $4,277,029
	Total: $20M	**Total: $2,201,159**	**Total: $17,798,841**
2020	**$20M** for Vision Research	**Withholds** USAMRDC: $386,740 SBIR/STTR: $663,000 **Budgeted Management Costs** $1,300,000 7%	**Research** Budgeted Peer-Reviewed Research: $17,650,260
	Total: $20M	**Total: $2,349,740**	**Total: $17,650,260**

The following abbreviations are used for withholds:
USAMRDC: US Army Medical Research and Development Command
SBIR/STTR: Small Business Innovation Research/Small Business Technology Transfer
Percent of management costs=management costs/(appropriation-withholds)

Table B-36. FY19 Defense Medical Research and Development Restoral Program CDMRP Executed Funds, Management Costs, and Execution of Investment Strategy

Fiscal Year	CDMRP Executed Funds	Management Costs	Investment Strategy
2019	**$44.6M** for Defense Medical Research and Development from the Guidance for the Development of the Force Funding	**Management Costs** $215,791 0.48%	**Research** Military Infectious Diseases Awards: $28,235 Military Operational Medicine Awards: $3,637,661 Combat Casualty Care Awards: $7,304,073 Clinical and Rehabilitative Medicine Awards: $30,600,010 Accelerating Innovation in Military Medicine Research Award: $2,857,019
	Total: $44.6M	**Total: $215,791**	**Total: $44,426,998**

Percent of management costs=management costs/(appropriation-withholds)

Table B-37. FY19 Defense Medical Research and Development Program CDMRP Executed Funds, Management Costs, and Execution of Investment Strategy

Fiscal Year	CDMRP Executed Funds	Management Costs	Investment Strategy
2019	**$99.01M** for Defense Medical Research and Development from the Guidance for the Development of the Force Funding	**Management Costs** $12,719,943 12.85%	**Research** Medical Simulation and Information Sciences Awards: $3,705,464 Military Infectious Diseases Awards: $5,358,927 Military Operational Medicine Awards: $4,413,764 Combat Casualty Care Awards: $46,901,016 Clinical and Rehabilitative Medicine Awards: $25,907,899
	Total: $99.01M	**Total: $12,719,943**	**Total: $86,287,070**

Percent of management costs=management costs/(appropriation-withholds)

Table B-38. FY19 Psychological Health/Traumatic Brain Injury Research Program
CDMRP Executed Funds, Management Costs, and Execution of Investment Strategy

Fiscal Year	CDMRP Executed Funds	Management Costs	Investment Strategy
2019	**$59.94M** for Psychological Health and Traumatic Brain Injury Research	**Management Costs** $4,219,000 7.04%	**Research** Broad Agency Announcement for Extramural Medical Research: $7,008,165 Complex Traumatic Brain Injury Rehabilitation Research - Clinical Research Award: $6,000 Complex Traumatic Brain Injury Rehabilitation Research - Clinical Trial Award: $12,155,648 Complex Traumatic Brain Injury Rehabilitation Research Award - Funding Level 2: $50,000 Complex Traumatic Brain Injury Rehabilitation Research Clinical Research Award - Human Subjects: $965,676 Comprehensive Universal Prevention /Health Promotion Interventions Award - Clinical Trial: $395,400 Federal Interagency Traumatic Brain Injury Research Analysis Award: $4,741,676 Long-Term Impact of Military - Related Brain Injury Consortium Award: $6,765,818 Medical Research Award: $1,121,927 Multi-Domain Lifesaving Trauma Innovations Award: $2,721,928 OTA: $2,806,701 Pain Management Collaboratory - Pragmatic Clinical Trials Demonstration Projects: $674,983 Precision Trauma Care Research Award: $6,854,492 Precision Trauma Care Research Award - Clinical Trial: $2,196,140 Prevention Research to Reduce Sexual Assault and/or Understand Adjustment Disorders Investigator-Initiated Focused Research Award: $6,317,391 Prolonged Field Care Research Award - Funding Level 2 - Preclinical Research: $102,940 Psychological Health Research Award: $21,925 Psychological Health Research Award-Partner PI Option: $794,900 Resilience and Readiness Optimization/Enhancement Translational Research Award: $18,279
	Total: $59.94M	**Total: $4,219,000**	**Total: $55,719,989**

Percent of management costs=management costs/(appropriation-withholds)

Table B-39. FY19 Armed Forces Institute of Regenerative Medicine
CDMRP Executed Funds, Management Costs, and Execution of Investment Strategy

Fiscal Year	CDMRP Executed Funds	Management Costs	Investment Strategy
2019	**$7.70M** for Armed Forces Institute of Regenerative Medicine	**Management Costs**	**Research** Focus Area Research: $7,703,481
	Total: $7.70M		**Total: $7,703,481**

Table B-40. FY19 Regenerative Medicine Focused Research Award
CDMRP Executed Funds, Management Costs, and Execution of Investment Strategy

Fiscal Year	CDMRP Executed Funds	Management Costs	Investment Strategy
2019	**$19.99M** for Regenerative Medicine Focused Research	**Management Costs**	**Research** Muscle Regeneration: $10,253,360 Peripheral Nerve Regeneration: $9,744,795
	Total: $19.99M		**Total: $19,998,155**

Table B-41. FY19 Small Business Innovation Research/Small Business Technology Transfer
CDMRP Executed Funds, Management Costs, and Execution of Investment Strategy

Fiscal Year	CDMRP Executed Funds	Management Costs	Investment Strategy
2019	**$31.37M** for Small Business Innovation Research/Small Business Technology Transfer Research	**Management Costs**	**Research** Small Business Innovation Research: $28,206,313 Small Business Technology Transfer: $3,161,653
	Total: $31.37M		**Total: $31,367,966**

Table B-42. FY19 Clinical Research Intramural Initiative
CDMRP Executed Funds, Management Costs, and Execution of Investment Strategy

Fiscal Year	CDMRP Executed Funds	Management Costs	Investment Strategy
2019	**$13.77M** for Clinical Research Intramural Initiative	**Infrastructure Support Services** $11,469,031	**Research** Investigator-Initiated Research Award: $1,996,214 Military Performance Optimization Research Award: $740,000 Military Performance Optimization Research Award - Clinical Trial: $558,000 Military Women's Health Research Award: $1,112,000
	Total: $13.77M	**Total: $11,469,031**	**Total: $4,406,214**

Percent of management costs=management costs/(appropriation-withholds)

APPENDIX C: BREAST CANCER RESEARCH SEMIPOSTAL AWARDS FY99-FY19

Fiscal Year	Principal Investigator	Amount	Institution	Proposal Title
FY99	Roger Daly	$283,649	Garvan Institute	Identification of Novel Prognostic Indicators for Breast Cancer through Analysis of the EMS1/ Cortactin Signaling Pathway
	Thomas Deuel	$5,000[1]	Scripps Institute	Novel Angiogenic Domains: Use in Identifying Unique Transforming and Tumor-Promoting Pathways in Human Breast Cancer
	Wolf Heyer	$111,444	University of California, Davis	In Vitro Recombination Activities of the Breast Cancer Predisposition Protein BRCA2
	Elizabeth Musgrove	$222,652	Garvan Institute	Role of Cyclin D1 and p27 in Steroidal Control of Cell Cycle Progression in the Mammary Gland in Vivo
	Sudhir Shah	$279,000	University of Arkansas	Role of a Novel Matrix-Degrading Metalloproteinase in Breast Cancer Invasion
	Lihong Wang	$317,510	Texas A&M University	Scanning Microwave-Induced Acoustic Tomography
	Michael White	$334,094	University of Texas Southwest Medical Center	Isolation of Factors that Disrupt Critical Protein/ Protein Interactions Within the Telomerase Holoenzyme for Use in Breast Cancer Therapeutics
	Daniel Wreschner	$225,000	Tel Aviv University	Analysis of the Secreted Novel Breast Cancer-Associated MUC1/Zs Cytokine
FY00	Eileen Adamson	$578,183	Burnham Institute	Cripto: A Target for Breast Cancer Treatment
	Emmanuel Akporiaye	$454,500	University of Arizona	Tumor-Mediated Suppression of Dendritic Cell Vaccines
	Linda Penn	$296,142	University of Toronto	Exploiting the Novel Repressed Transactivator Assay to Identify Protein Interactors and Peptide Inhibitors of the Myc Oncoprotein
FY01	Qiuyin Cai	$560,144	Vanderbilt University	Genetic Polymorphisms, Mitochondrial DNA Damage, and Breast Cancer Risk
	Kermit Carraway	$427,225	University of California, Davis	Identification of a Functional Human Homolog of Drosophila Kek1, an Inhibitor of Breast Tumor Cell Growth
	Preet Chaudhary	$312,000	University of Texas Southwest Medical Center	The Role of Ectodysplasin A (EDA) and Its Receptors in the Pathogenesis of Breast Cancer
	Robert Geahlen	$425,425	Purdue University	Characterization of Syk in Breast Carcinoma Cells
	William Rosner	$454,181	St. Luke's-Roosevelt Hospital Center	Autocrine and Paracrine Control of Breast Cancer Growth by Sex Hormone-Binding Globulin
FY02	Q. Ping Dou	$491,999	Wayne State University	Synthetic Beta-Lactam Antibiotics as a Selective Breast Cancer Cell Apoptosis Inducer: Significance in Breast Cancer Prevention and Treatment
	Andrew Godwin	$504,000	Fox Chase Cancer Center	The Nuclear Death Domain Protein p84N5, a Candidate Breast Cancer Susceptibility Gene
	Archibald Perkins	$490,500	Yale University	Rapid Genomic Approach to Cancer Gene Discovery in Breast Cancer

Fiscal Year	Principal Investigator	Amount	Institution	Proposal Title
FY03	Gina Chung	$490,447	Yale University	Quantitative In Situ Assessment of the Somatostatin Receptor in Breast Cancer to Assess Response to Targeted Therapy with 111-in-Pentetreotide
	Rudolf Kaaks	$367,639	German Cancer Research Center (DKFZ)	Fatty Acid Synthesis Gene Variants and Breast Cancer Risk: A Study Within the European Prospective Investigation into Cancer and Nutrition (EPIC)
	Paul Yaswen	$508,790	Lawrence Berkeley National Laboratory	Functional Analysis of BORIS, a Novel DNA-Binding Protein
	Elad Ziv	$767,171	University of California, San Francisco	Admixture and Breast Cancer Risk Among Latinas
FY04	Mina Bissell	$386,569	Lawrence Berkeley National Laboratory	Use of HA-Metal Nanoparticles to Identify and Characterize Tumorigenic Progenitor Cell Subsets in Breast Tumors
	Christina Clarke	$588,738	Northern California Cancer Center	The Hygiene Hypothesis and Breast Cancer: A Novel Application of an Etiologic Theory for Allergies, Asthma, and Other Immune Disorders
	Todd Giorgio	$453,000	Vanderbilt University	Surface Functionalized Nanoparticles and Nanocrystals for Proximity-Modulated, Early Neoplasia Detection, Imaging, and Treatment of Breast Cancer
	Mark Lemmon	$475,500	University of Pennsylvania	Harnessing Novel Secreted Inhibitors of EGF Receptor Signaling for Breast Cancer Treatment
FY05	Kurt Zinn[2]	$436,500	University of Alabama at Birmingham	Novel Screening and Precise Localization of Early Stage Breast Cancer in Animal Model
	Xin-Yun Huang	$483,600	Cornell University, Weill Medical College	Migrastatin Analogues as Potent Inhibitors of Breast Cancer Metastasis
	Yang Liu	$448,500	Ohio State University	Hunting for Novel X-Linked Breast Cancer Suppressor Genes in Mouse and Human
	Jianghong Rao	$468,000	Stanford University	Ribozyme-Mediated Imaging of Oncogene Expression in Breast Tumor Cells
FY06	Gayathri Devi	$155,085[3]	Duke University Medical Center	Modulation of Regulatory T Cells as a Novel Adjuvant for Breast Cancer Immunotherapy
	Amy Lee	$489,000	University of Southern California	A New Mechanism for Estrogen-Starvation Resistance in Breast Cancer
	Yi Li	$438,455	Baylor College of Medicine	The ER/PR Status of the Originating Cell of ER-Negative Breast Cancer
	Shaker Mousa	$377,620	Albany College of Pharmacy	Enhancing the Efficacy of Chemotherapeutic Breast Cancer Treatment with Non-Anticoagulant Heparins
	Fraydoon Rastinejad	$454,500	University of Virginia	Structural Characterization of the Interdomain Features of the Estrogen Receptor
FY07	Charlotte Kuperwasser	$817,500	Tufts University	Mechanisms of Breast Cancer Associated with Obesity
	Kimberly Kelly	$244,450[4]	University of Virginia	Genetically Encoded Targeted, Amplifiable, Imaging Agents for Early Detection of Breast Cancer
	Susan Gerbi	$155,550[5]	Brown University	Hormonal Involvement in Breast Cancer Gene Amplification

Fiscal Year	Principal Investigator	Amount	Institution	Proposal Title
FY08	Chung Park	$111,663	North Dakota State University	In Utero Exposure to Dietary Methyl Nutrients and Breast Cancer Risk in Offspring
	Maciej Radosz	$528,939	University of Wyoming	Breast Cancer-Targeting Nuclear Drug Delivery Overcoming Drug Resistance for Breast Cancer Therapy
	Ann Hill	$577,500	Oregon Health and Science University	Vaccine Vector for Sustained High-Level Antitumor CTL Response
	Youngjae You	$503,666	University of Oklahoma Health Science Center	Targeted Delivery and Remote-Controlled Release of Chemotherapeutic Agents
	Tiffany Seagroves	$166,667[6]	University of Tennessee Health Science Center	The Role of HIF-1 Alpha in Breast Cancer: A Positive Factor in Cancer Stem Cell Expansion via Notch?
FY09	Peggy Reynolds	$730,000[7]	Cancer Prevention Institute of California	Hazardous Air Pollutants and Breast Cancer: An Unexplored Area of Risk
	John Wysolmerski	$620,626	Yale University	Effects of Nuclear Parathyroid Hormone-Related Protein Signaling in Breast Cancer
FY10	Pepper Schedin	$368,125[8]	University of Colorado, Denver	The Immune Modulatory Program of Post-Partum Involution Promotes Pregnancy-Associated Breast Cancer
	Anthony Leung	$556,875[9]	Johns Hopkins University	The Role of Poly(ADP-Ribose) in microRNA Activity in Breast Cancers
FY11	Andy Minn	$399,942	University of Pennsylvania	Regulation of Metastasis and DNA Damage Resistance Pathways by Transposable Elements
	Xiaosong Wang	$409,693	Baylor College of Medicine	Copy Number Signature of Recurrent Gene Fusions Reveals Potential Drug Targets in Invasive Breast Cancer
	Susana Gonzalo Hervas	$58,975[10]	St. Louis University	Stabilization of 53BP1 in Triple-Negative and BRCA-Deficient Breast Tumors: A Novel Therapeutic Strategy
FY12	Jing Yang	$465,000	University of California, San Diego	Regulation of Breast Cancer Stem Cell by Tissue Rigidity
	Filippo Giancotti	$174,837[11]	Memorial Sloan-Kettering Cancer Center	Autophagy and TGF-Beta Antagonist Signaling in Breast Cancer Dormancy at Premetastatic Sites
FY13	Seth Rubin	$457,075	University of California, Santa Cruz	Inhibition of Retinoblastoma Protein Inhibition
	Geoffrey Luke	$96,992[12]	Dartmouth College	Noninvasive Label-Free Detection of Micrometastases in the Lymphatics with Ultrasound-Guided Photoacoustic Imaging
FY14	Dan Shu	$364,343	Ohio State University	Ultrastable Nontoxic RNA Nanoparticles for Targeting Triple-Negative Breast Cancer Stem Cells
	Leif Ellisen	$93,050[13]	Massachusetts General Hospital	Defining High-Risk Precursor Signaling to Advance Breast Cancer Risk Assessment and Prevention
	Edward Brown	$7,457[14]	University of Rochester	Prediction of Metastasis Using Second Harmonic Generation
	David DeNardo	$7,061[15]	Washington University	Reprogramming the Metastatic Microenvironment to Combat Disease Recurrence
FY15	Ricardo Bonfil	$254,765[16]	Wayne State University	Discoidin Domain Receptors: Novel Targets in Breast Cancer Bone Metastasis
	Carl Maki	$254,765[17]	Rush University Medical Center	Targeting Prolyl Peptidases in Triple-Negative Breast Cancer

Fiscal Year	Principal Investigator	Amount	Institution	Proposal Title
FY16	Sridhar Mani	$174,992[18]	Albert Einstein College of Medicine	Inhibition of Microbial Beta-Glucuronidase as a Strategy Toward Breast Cancer Chemoprevention
	Sophie Lelievre	$353,879[19]	Purdue University	Risk-on-a-Chip for Tailored Primary Prevention of Breast Cancers
FY17	Jogender Tushir-Singh	$282,378[20]	University of Virginia	A Highly Superior and Selective Cancer Immunotherapy-Based Approach for Triple-Negative Breast Cancers
	Pradeep Chaluvally-Raghavan	$282,378[21]	Medical College of Wisconsin	Targeting miR551b to Prevent Tumor Formation and Metastasis of Triple-Negative Breast Cancer
FY18	David Potter	$263,717[22]	University of Minnesota, Twin Cities	Potentiation of Immune Checkpoint Blockade by Inhibition of Epoxyeicosatrienoic Acid-Driven Tumor Respiration
	Abhishek Sharma	$263,716[23]	Stevens Institute of Technology	A Novel Class of Antagonists for Robust Inhibition of Mutant Estrogen Receptor Action in Endocrine-Resistant Metastatic Breast Cancer
FY19	Jeffrey Frost	$295,109[24]	University of Texas Health Science Center at Houston	Targeting the Tumor Microenvironment and Metastatic Niche in Breast Cancer
	Hannah Rabinowich	$295,110[25]	University of Pittsburgh	A New Persistence Mechanism for Drug-Tolerant Breast Cancer Cells

[1] Total award amount was $404,176; remaining funds were from the FY99 BCRP.
[2] The original Principal Investigator, Dr. Tandra Chaudhuri, is deceased.
[3] Total award amount was $461,933; remaining funds were from the FY06 BCRP.
[4] Total award amount was $687,397 remaining funds were from the FY06 BCRP.
[5] Total award amount was $787,325; remaining funds were from the FY06 and FY07 BCRP.
[6] Total award amount was $554,987; remaining funds were from the FY08 BCRP.
[7] Total award amount was $860,883; remaining funds were from the FY09 BCRP.
[8] Total award amount was $556,028; remaining funds were from the FY10 BCRP.
[9] Total award amount was $585,652; remaining funds were from the FY10 BCRP.
[10] Total award amount was $744,661; remaining funds were from the FY11 BCRP.
[11] Total award amount was $331,449; remaining funds were from the FY12 BCRP.
[12] Total award amount was $497,288; remaining funds were from the FY13 BCRP.
[13] Total award amount was $605,208; remaining funds were from the FY14 BCRP.
[14] Total award amount was $215,628; remaining funds were from the FY14 BCRP.
[15] Total award amount was $527,797; remaining funds were from the FY14 BCRP.
[16] Total award amount was $522,715; remaining funds were from the FY15 BCRP.
[17] Total award amount was $581,250; remaining funds were from the FY15 BCRP.
[18] Total award amount was $626,252; remaining funds were from the FY16 BCRP.
[19] Total award amount was $564,673; remaining funds were from the FY16 BCRP.
[20] Total award amount was $573,784; remaining funds were from the FY17 BCRP.
[21] Total award amount was $563,272; remaining funds were from the FY17 BCRP.
[22] Total award amount was $567,344; remaining funds were from the FY18 BCRP.
[23] Total award amount was $471,719; remaining funds were from the FY18 BCRP.
[24] Total award amount was $693,001; remaining funds were from the FY19 BCRP.
[25] Total award amount was $704,250; remaining funds were from the FY19 BCRP.

APPENDIX D: ACRONYMS

3D ..... three-dimensional
AAK1 ..... AP2-associated protein kinase 1
AD ..... Alzheimer's disease
ADNI ..... Alzheimer's Disease Neuroimaging Initiative
ADPKD ..... autosomal dominant polycystic kidney disease
ADRD ..... AD and related dementia
AFIRM ..... Armed Forces Institute of Regenerative Medicine
AI ..... Artificial Intelligence
ALM ..... acral lentiginous melanoma
ALS ..... amyotrophic lateral sclerosis
ALSRP ..... Amyotrophic Lateral Sclerosis Research Program
ARP ..... Autism Research Program
ASADRP ..... Alcohol and Substance Abuse Disorders Research Program
ASD ..... autism spectrum disorder
ASUDs ..... Alcohol and Substance Use Disorders
B ..... billion
BAAs ..... Broad Agency Announcements
BADER ..... Bridging Advanced Developments for Exceptional Rehabilitation
BAL ..... blood alcohol levels
BAT ..... Bipolar androgen therapy
BCBT ..... Brief Cognitive Behavioral Therapy
BCL-2 ..... B-cell lymphoma 2
BCL-XL ..... B-cell lymphoma extra-large
BCRP ..... Breast Cancer Research Program
BCRS ..... Breast Cancer Research Semipostal
BMF ..... bone marrow failure
BMFRP ..... Bone Marrow Failure Research Program
CA ..... Concept Award
CAIX ..... Carbonic Anhydrase IX
CAP ..... Consortium to Alleviate Post-Traumatic Stress Disorder
CAR ..... Chimeric Antigen Receptor
CARE ..... Concussion Assessment, Research, and Education
CBT-I ..... cognitive behavior therapy for insomnia
CCCRP ..... Combat Casualty Care Research Program
ccRCC ..... clear cell carcinoma
CDEs ..... Common Data Elements
CDMRP .... Congressionally Directed Medical Research Programs
CDNF ..... cerebral dopamine neurotrophic factor
CEaD ..... Communicated Effectively about Donation
CENC ..... Chronic Effects of Neurotrauma Consortium
CHIP ..... clonal hematopoiesis of indeterminate potential
CI ..... cochlear implant
CPMRP ..... Chronic Pain Management Research Program
CRDA ..... Clinical Research Development Award
CRED ..... Combat-Ready Exposure Device
CRII ..... Clinical Research Intramural Initiative
CriSP ..... Cold Stored Platelet Early Intervention
CriSP-HS ..... cold stored platelets in patients in hemorrhagic shock
CRMRP .. Clinical and Rehabilitative Medicine Research Program
CRPC ..... castration-resistant prostate cancer
CRRP ..... Combat Readiness – Medical Research Program
CSI ..... cytokine signaling index
CURE ..... Citizens United for Research in Epilepsy
DART ..... dual antigen recognition technology
DECAMP ..... Detection of Early Lung Cancer Among Military Personnel
DHA ..... Defense Health Agency
DHP ..... Defense Health Program
DMD ..... Duchenne muscular dystrophy
DMDRP ..... Duchenne Muscular Dystrophy Research Program
DMPs ..... Disease Management Protocols
DMRDP ... Defense Medical Research and Development Program
DOD ..... Department of Defense
DUE DARE ..... Dense Urban Environment Dosimetry for Actionable Information and Recording Exposure
EACE ..... Extremity Trauma and Amputation Center of Excellence
eBRAP ..... Electronic Biomedical Research Application Portal
FCAD ..... Fontan Circulation Assist Device
ECIs ..... Early-Career Investigators
ECM ..... Extracellular Matrix
EGS ..... Electronic Grants System
ER ..... endoplasmic reticulum
eRA ..... Electronic Research Administration
ERP ..... Epilepsy Research Program
FCM ..... focal cortical malformation
FDA ..... US Food and Drug Administration
FY ..... fiscal year
FITBIR ..... Federal Interagency Traumatic Brain Injury Research
FPT 5-fluorophenyl-2-aminotetralin
FTTSA ..... Focused Translational Team Science Award
GAK ..... G-associated kinase
GI ..... gastrointestinal
GPCC ..... Georgia Prostate Cancer Coalition
GR ..... glucocorticoid receptor
GWI ..... Gulf War Illness
GWICTIC ..... Gulf War Illness Clinical Trials and Interventions Consortium

GWIRP .....Gulf War Illness Research Program
HGSCs .....high-grade serous carcinomas
HHS ..... US Department of Health and Human Services
HITI .....Health Information Technologies/Informatics
HPV .....human papillomavirus
HRRP .....Hearing Restoration Research Program
HSCs ..... hematopoietic stem cells
HSPCs .....hematopoietic stem and progenitor cells
IDA .....Idea Development Award
IED ..... improvised explosive device
IFNγ ..... interferon gamma
IND .....Investigational New Drug
IOM .....Institute of Medicine
IR-CARs ..... immune restoring CARs
ITEA ..... Innovative Treatment Evaluation Award
JHU .....Johns Hopkins University
JPCs .....Joint Program Committees
JWMRP .....Joint Warfighter Medical Research Program
KCRP ..... Kidney Cancer Research Program
LAM ..... Lymphangioleiomyomatosis
LCN .....lacunocanalicular network
LCRP..... Lung Cancer Research Program
LIMBIC..... Long-Term Impact of Military-Relevant Brain Injury Consortium
LITES ..... Linking Investigations in Trauma and Emergency Services
LOC ..... Lab-on-Chip
LRP.....Lupus Research Program
M..... million
MAST.....Medical Assist Support Technologies
MBRP .....Military Burn Research Program
MDS .....myelodysplastic syndromes
MedSim .....Medical Simulation
METRC.....Major Extremity Trauma Research Consortium
MHINT.....Military Hearing In Noise Test
micro-OCT.....micro-optical coherence tomography
MIDRP ..... Military Infectious Diseases Research Program
MilSINT.....Military Sound in Noise Test
MLKIs ..... multiple ligament knee injuries
MOA .....Memorandum of Agreement
MOMRP ..... Military Operational Medicine Research Program
MRI.....magnetic resonance imaging
MRP.....Melanoma Research Program
MS.....multiple sclerosis
MSISRP ..... Medical Simulation and Information Sciences Research Program
MSRC .....Military Suicide Research Consortium
MSRP .....Multiple Sclerosis Research Program
MTA ..... methylthioadenosine
mTBI .....mild traumatic brain injury
MTFs.....Military Treatment Facilities
MW-VC..... Manual Wheelchair Virtual Coach
NCAA.....National Collegiate Athletic Association
NCORP..... NCI Community Oncology Research Program
NET..... Neoadjuvant Endocrine Therapy
NETP..... Neurotoxin Exposure Treatment Parkinson's
NF .....neurofibromatosis
NFCTC..... Neurofibromatosis Clinical Trials Consortium
NFRP .....Neurofibromatosis Research Program
NIH ..... National Institutes of Health
NMCP .....Naval Medical Center Portsmouth
NMT..... NeoMatrix Therapeutics, Inc.
NSCLC ..... Non-Small Cell Lung Cancer
NSU.....Nova Southeastern University
OA ..... osteoarthritis
OASD(HA) ..... Office of the Assistant Secretary of Defense for Health Affairs
OCA ..... Ovarian Cancer Academy
OCRP .....Ovarian Cancer Research Program
OMICS-CDA .....Omics Consortium Development Awards
OPO..... Organ Procurement Organization
OPORP.. Orthotics and Prosthetics Outcomes Research Program
ORP .....Office of Research Protections
ORRCA..... Outer Retina Reconstruction for Combat Afflictions
OTAs .....Other Transaction Agreements
OUD..... opioid use disorder
OXPHOS..... oxidative phosphorylation
PACT.....Prehospital Airway Control Trial
PADs..... Program Area Directorates
PAIN ..... Prehospital Analgesia INterventional
PASA .....Pharmacotherapies for Alcohol and Substance Abuse
PCARP ..... Pancreatic Cancer Research Program
PCBN..... Prostate Cancer Biorepository Network
PCCTC..... Prostate Cancer Clinical Trials Consortium
PCRP .....Prostate Cancer Research Program
PD ..... Parkinson's disease
PDPN..... podoplanin
PH ..... psychological health
PH/TBIRP ..... Psychological Health and Traumatic Brain Injury Research Program
PIs .....Principal Investigators
PLR.....perilacunar/canalicular remodeling
PMC.....Pain Management Collaboratory
PMS..... progressive MS
PRARP .....Peer Reviewed Alzheimer's Research Program
PRCRP .....Peer Reviewed Cancer Research Program

PRMRP ..... Peer Reviewed Medical Research Program
PRORP ..... Peer Reviewed Orthopaedic Research Program
PTE ..... post-traumatic epilepsy
PTH ..... post-traumatic headache
PTSD ..... post-traumatic stress disorder
RA ..... Rheumatoid arthritis
R&A ..... Review and Analysis
R&D ..... research and development
RCC ..... renal cell carcinoma
RCDA ..... Resource and Community Development Award
RCRP ..... Rare Cancer Research Program
RCT ..... Randomized Controlled Trial
RDT&E ..... Research, Development, Test, and Evaluation
RFI ..... request for information
RHERP ..... Radiation Health Effects Research Program
RRMS ..... relapsing remitting MS
RS fMRI ..... resting state functional MRI
RTF ..... retinal thermofusion
rTMS ..... repetitive Transcranial Magnetic Stimulation
RTRP ..... Reconstructive Transplant Research Program
SAA ..... Severe Aplastic Anemia
SBIR ..... Small Business Innovation Research
scFvs ..... single chain variable region fragment
SCIs ..... Spinal cord injuries
SCIRP ..... Spinal Cord Injury Research Program
SCS ..... Scientific Classification System
SLE ..... systemic lupus erythematosus
SNHL ..... sensorineural hearing loss
SRP ..... Scleroderma Research Program
STaR ..... Surgical Timing and Rehabilitation
STIC ..... serous tubal intraepithelial carcinoma
STTR ..... Small Business Technology Transfer
SWAT ..... Shock, Whole Blood, and Assessment of TBI
TAPTE ..... Team Approach to the Prevention and Treatment of Post-Traumatic Epilepsy
TBDRP ..... Tick-Borne Disease Research Program
TBDs ..... tick-borne diseases
TBI ..... traumatic brain injury
TCRP ..... Trauma Clinical Research Program
TED ..... TBI Endpoints Development
TERT ..... telomerase reverse transcriptase gene
TIC ..... trauma-induced coagulopathy
TNBC ..... Triple-Negative Breast Cancer
TQIP ..... Trauma Quality Improvement Program
TRAIN ..... TSC Remote Assessment and Intervention
Treg ..... Regulatory T
TRIAGE ..... Trauma Resiliency Immersive Adaptive Gaming Environment
TSC ..... tuberous sclerosis complex
TSC-LAM ..... tuberous sclerosis associated lymphangioleiomyomatosis
TSCRP ..... Tuberous Sclerosis Complex Research Program
USAMRAA ..... US Army Medical Research Acquisition Activity
USAMRDC ..... US Army Medical Research and Development Command
UV ..... ultraviolet radiation
VA ..... US Department of Veterans Affairs
VCA ..... vascularized composite allotransplantation
VEGFR ..... vascular endothelial growth factor receptor
VRP ..... Vision Research Program
VSs ..... vestibular schwannomas
WET ..... whole-eye transplantation

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September 30, 2020