2019 ANNUAL REPORT

Congressionally Directed Medical Research Programs

CDMRP
Department of Defense

US Army Medical Research and Development Command

Letter from the Director

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

As the new Director of the Congressionally Directed Medical Research Programs (CDMRP), I am pleased to present to you the 2019 Annual Report. This report reflects the efforts of over 30 distinct research programs aimed at supporting scientific breakthroughs that will transform healthcare for Service members and the American public. I am focused on our mission to responsibly manage innovative and impactful research that will lead to health care solutions by utilizing best practices and transparent processes. The success of our programs as detailed in the annual report is a direct result of collaborations and partnerships with consumers, scientists, clinicians, professional organizations, academia, and military communities. I encourage you to read this report and learn about our history, program facts, funding profiles, the numbers and types of research projects awarded, and specific highlights for each program. On behalf of the entire CDMRP team, we look to continue the legacy of funding groundbreaking, paradigm-shifting research that will lead to cures or improvements in patient care and prevention of diseases and injuries over the coming years.

Sincerely,

Stephen

Colonel Stephen J. Dalal, DVM, MPH
US Army, Veterinary Corps
Director, CDMRP

Department of Defense
US Army Medical Research and Development Command
Congressionally Directed Medical Research Programs
Annual Report
September 30, 2019

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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

Introduction

History and Overview

Congressionally Directed Medical Research Programs (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 has evolved into 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 manages individual research programs focused on military medical research, cancer research, and other disease- 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 overseas 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 DOD Army Futures Command and within US Army Medical Research and Development Command (USAMRDC). USAMRDC's mission is to responsively and responsibly create, develop, deliver, and sustain medical capabilities for the Warfighter. To accomplish this mission, USAMRDC leads the advancement of military medicine through innovative management and efficient execution of allocated funding (read more about USAMRDC under Military Partnerships on page 12). Since its first appropriation of Congressional funding in fiscal year 1992 (FY92), CDMRP has been responsible for managing more than $14.4 billion (B) in Defense appropriations.

Fiscal Year 2019

In FY19, CDMRP provided management and oversight for its 30 FY18 research programs. In addition, Congress added three new programs in FY19: the Chronic Pain Management Research Program (page 42), the Combat Readiness-Medical Research Program (page 46), and the Melanoma Research Program (page 64). **Figure 1** shows research funding managed by CDMRP over the last 10 years.

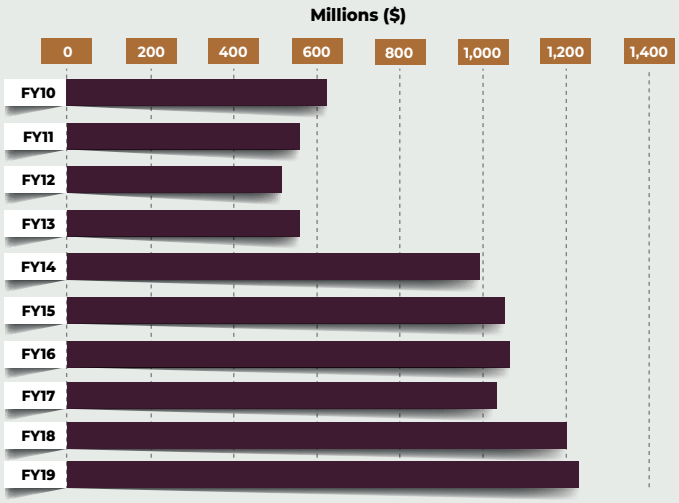
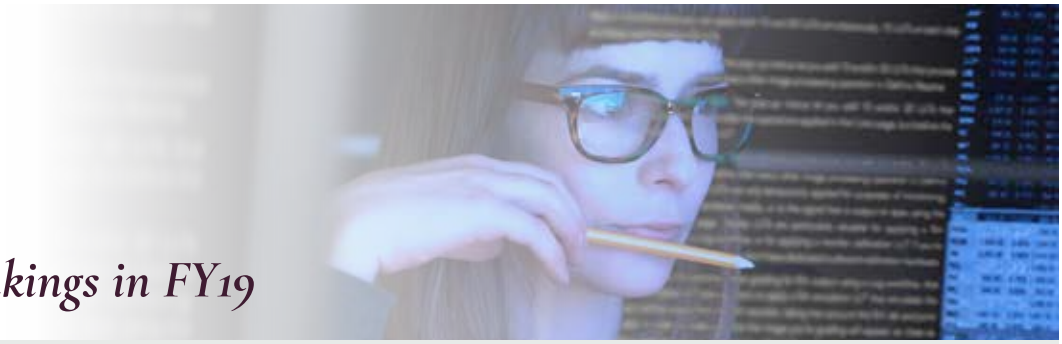


Figure 1. FY10–FY19 Research Funding



Major Undertakings in FY19

National Academy of Medicine Review

Since its inception, CDMRP has followed guidance from the Institute of Medicine (IOM), now called the Health and Medicine Division of the National Academy of Medicine (NAM). The highly regarded two-tier review process utilized by CDMRP to review applications is based on recommendations made by the IOM in 1993 ("Strategies for Managing the Breast Cancer Program: A Report to the US Army Medical Research and Development Command," 1993).

In 2014 the Senate Appropriations Committee directed the DOD to contract with the NAM to conduct a study of CDMRP's two-tier review process and coordination of research priorities with the National Institutes of Health (NIH). The goal of this assessment was to identify how well the two-tier review processes and coordination efforts were working and whether there may be areas that could be improved. In addition to the review of the two-tier program cycle, the NAM committee assessed the coordination of CDMRP with NIH and the US Department of Veterans Affairs (VA). A full report from the NAM on CDMRP's two-tier review process and coordination efforts was published in November 2016. The NAM committee recommended areas for improvement, but found overall that the CDMRP review process was effective in allocating funding within each research program and also noted that, "the inclusion of consumers in both tiers of the review is a positive aspect of the CDMRP review process that can benefit scientists and consumers alike." CDMRP appreciates the evaluation and viewpoints of the ad hoc NAM committee and continues to integrate their findings and recommendations as part of our ongoing efforts to improve the CDMRP review process and strengthen coordination with NIH and VA.

As part of their final report, the NAM recommended that each CDMRP program "…develop a strategic plan that identifies and evaluates research foci, benchmarks for success, and investment opportunities for 3-5 years into the future" and that these strategic plans "should specify the mission of the program, coordination activities with other organizations, research priorities, how those priorities will be addressed by future award mechanisms, how research outcomes will be tracked, and how outcomes will inform future research initiatives." In response to the NAM recommendations, CDMRP programs conducted strategic planning in conjunction with our FY18 Vision Setting meetings. As a result, CDMRP programs developed Strategic Plan documents, which are publically available on individual program pages of CDMRP's website. Each program's Strategic Plans will be revisited at the yearly Vision Setting meetings and updated as needed.

CDMRP Strategic Plan

Since its founding in 1992, CDMRP has grown from a single research program into a global organization that supports research across over 30 distinct programs, each of which are tasked to fund biomedical research in response to the unique needs of their stakeholders. Despite the organization's growth over the years, all programs share the common goal of advancing paradigm shifting research that will lead to cures or improvements in patient care. During execution of its vision and mission, CDMRP retains a focus on its core values of integrity, collaboration, and service to effectively and efficiently meet the medical needs of Service members, Veterans, and their families.

Section 736 of the John S. McCain National Defense Authorization Act for FY19 (Public Law 115-232) directed the DOD to produce a strategic medical research plan that describes DOD medical research Focus Areas, medical research projects, coordination processes across defense medical research and development (R&D) to ensure alignment with mission, promote synergy, address gaps, and minimize duplication, and efforts to coordinate with other departments and agencies of the federal government. As part of this broader DOD-wide effort, and in keeping with the spirit of the NAM recommendations, CDMRP has developed a strategic plan that describes the overarching guiding principles and goals for CDMRP to continuously improve its performance and outcomes, to fulfil the vision and mission of the organization.

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 112 FY18 funding opportunities, eBRAP received and processed over 11,150 pre-applications and over 6,600 full applications. During FY19, eBRAP is managing about 120 funding opportunities, with pre-application and full application receipts extending from March 2019 through December 2019.

eBRAP Highlights:

- Streamlines operational efficiency and effectiveness in retrieving and processing research applications from grants.gov through increased automation and greater data integrity.
- Is the front-end interface for bilateral communication with the research community in over 109 countries.
- Provides worldwide web-based accessibility for receipt and processing of pre-applications, full applications, and documents required for award negotiations, and management of research protections and award performance/ accomplishments 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 (PA).
- Provides functionality to the military medical community by directly accepting DOD intramural application submissions, which is not supported by Grants.gov.
- Interfaces directly with Grants.gov for retrieval, processing, and administrative review of extramural applications.
- Performs computer-automated processing, modification, and compliance of pre-application and proposal applications according to each PA.
- Provides capability to allow researchers to review and modify application components following submission.
- 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, servicing as the central repository of research data and conduit of information needed by other systems.

EGS Highlights:

- EGS enables real-time electronic workflows among USAMRDC offices, including USAMRAA, the Office of Surety, Safety and Environment, and the Office of Research Protections (ORP).
- Multiple user groups are able to collaborate, allowing data inputs, generating of reports, and performing daily administrative tasks associated with research award management and monitoring progress in a central, secure location.
- Research output including research results, products, and outcomes are captured and systematically categorized in customized modules to allow for analysis reporting to stakeholders and to respond to inquiries.

- Program evaluation functions allow for the ability to mine data for analysis of research output.
- System-to-system interfaces allow transfer of data between USAMRDC, DOD partner agencies, and contractor organizations which support various activities including peer and programmatic reviews.
- 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.
- Comprehensive workflows within EGS have enabled ORP to manage the complete life cycle of animal and human research protocols funded under CDMRP-managed awards and other DOD organizations.
- EGS supports data transfers to external systems, including the International Cancer Research Partnership and Federal RePORTER.
- Use of EGS has expanded to include management of DOD Intramural awards managed by several Joint Program Committees (JPCs)/Program Area Directorates (PADs) and other USAMRDC organizations.
- EGS supports continuous process improvement initiatives to enable users and CDMRP to become more efficient.

Federal RePORTER

Federal RePORTER (http://federalreporter.nih.gov) is a collaborative effort led by the Science and Technology for America's Reinvestment Measuring the EffecTs of Research on Innovation, Competitiveness and Science (STAR METRICS®) to create a publically available data repository of Federal Research and Development (R&D) investments. Through this initiative, a searchable database of funded scientific awards from the US Department of Health and Human Services (HHS), Department of Education, US Department of Agriculture (USDA), DOD, National Science Foundation (NSF), VA, Environmental Protection Agency (EPA), and National Aeronautics and Space Administration (NASA) has been created. Federal RePORTER utilizes some of its basic functions on a core set of data required from all Federal agencies, allowing analyses and comparisons to be performed. Current functionality includes the ability to search for similar projects using fingerprinting technology, in addition to mapping and charting capabilities. These features can be explored to conduct analysis of research topics for program-specific needs and collaboration. Additional features are in the planning stages. In response to US Government Accountability Office recommendations, CDMRP continued its efforts to support government transparency and engage the public, research community, and federal agencies by participating in the Federal RePORTER initiative. CDMRP-funded award data across all fiscal years are currently included in Federal RePORTER; new awards will be posted by the end of each fiscal year.

Our Programs

Highlights of FY18–FY19 programs managed and/or supported by CDMRP can be found within the program pages in this Annual Report, beginning on page 29. As detailed in **Table 1**, CDMRP successfully obligated FY18 appropriations across 30 programs encompassing 969 research awards. In addition, in FY19, CDMRP initiated the management of over $1.0B across 33 programs.

"My daughter was diagnosed at age 2.5 years with both autism and a major intellectual disability. Although I am an engineering professor, in 2000 I began shifting my research into looking at the causes of autism and how to best help people with autism. I have enjoyed serving as a reviewer for the Congressionally Directed Medical Research Programs for several years now. I especially like their focus, not just on great science, but also on innovation and impact, as well as their use of consumer reviewers. In 2016, our team was thrilled to be awarded an FY15 Clinical Trial Award from the Autism Research Program for treating gastrointestinal and autism symptoms in adults using Microbiota Transplant Therapy. I am excited by the progress we have made in successfully treating adults with autism and seeing the impact it has on improving their happiness and quality of life."

Dr. James Adams, Arizona State University

Table 1. CDMRP Programs, Appropriations, and Applications Received and Awarded in FY18-FY19

Research Programs Managed by the CDMRP	FY18				FY19	
	Funds Received (in millions)	Applications Received	Applications Funded	Funding Modifications Completed	Funds Received (in millions)	Applications Received to Date
Alcohol and Substance Abuse Disorders	$4.0			2	$4.0	
Amyotrophic Lateral Sclerosis	$10.0	72	11		$10.0	55
Autism	$7.5	71	8		$7.5	59
Bone Marrow Failure	$3.0	32	6		$3.0	27
Breast Cancer	$130.0	1,563	106	5	$130.0	
Breast Cancer Research Semipostal[1]	$0.6		1		$0.6	1,459
Chronic Pain Management[2]	n/a	n/a	n/a	n/a	$10.0	
Combat Readiness Medical Research[2]	n/a	n/a	n/a	n/a	$15.0	
Duchenne Muscular Dystrophy	$3.2	27	3		$3.2	
Epilepsy	$7.5	43	8		$7.5	29
Gulf War Illness	$21.0	84	22	1	$22.0	53
Hearing Restoration	$10.0	23	7		$10.0	
Joint Warfighter Medical[3]	$50.0	44	6	4	$50.0	55
Kidney Cancer	$15.0	197	29		$20.0	205
Lung Cancer	$14.0	374	29		$14.0	349
Lupus	$5.0	99	12	1	$5.0	116
Melanoma[2]	n/a	n/a	n/a	n/a	$10.0	
Military Burn	$8.0	2	2	1	$8.0	57
Multiple Sclerosis	$6.0	57	9	1	$6.0	65
Neurofibromatosis	$15.0	87	24	1	$15.0	61
Orthotics and Prosthetics Outcomes	$10.0	37	8		$10.0	34
Ovarian Cancer	$20.0	168	27	2	$20.0	180
Parkinson's	$16.0	78	16		$16.0	105
Peer Reviewed Alzheimer's	$15.0	80	21		$15.0	54
Peer Reviewed Cancer	$80.0	823	114		$90.0	673
Peer Reviewed Medical	$330.0	1,426	205	6	$350.0	1,405
Peer Reviewed Orthopaedic	$30.0	57	18	6	$30.0	67
Prostate Cancer	$100.0	504	102	16	$100.0	500
Reconstructive Transplant	$12.0	150	21		$12.0	30
Spinal Cord Injury	$30.0	124	17	1	$30.0	128
Tick-Borne Disease	$5.0	39	6	1	$5.0	63
Tuberous Sclerosis	$6.0	56	13	1	$6.0	47
Vision	$15.0	57	11	1	$20.0	
Additional Supported DOD Programs/Projects						
Armed Forces Institute of Regenerative Medicine II	$9.5			16	$7.7	
Defense Medical Research and Development	$103.7	199	38	38	$85.7	136
Defense Medical Research and Development CSI[4] Restoral	$40.5		18	7	$11.3	
Medical Technology Enterprise Consortium[2]	n/a	n/a	n/a	n/a	TBD	2
Psychological Health/Traumatic Brain Injury	$60.9	79	23	9	$56.8	54
Small Business Innovation Research/ Small Business Technology Transfer	$7.7	17	28	1	$1.6	33
Trauma Clinical	$10.0				$10.0	
Other Submission Processes						
USAMRDC - Broad Agency Announcement[5]		99				98
Total	**$1,211.1**	**6,768**	**969**	**121**	**$1,227.9**	**6,199**

[1] Breast Cancer Semipostal funds applications received and reviewed by the Breast Cancer Research Program (BCRP).

[2] New in FY19.

[3] Joint Warfighter Medical Execution Management Breakdown: 6 awards and 4 modifications managed by CDMRP; 0 awards and 0 modifications managed by USAMMDA; and 0 modifications managed by USAMMA.

[4] CSI: Congressional Special Interest

[5] CDMRP manages the application receipt and review process for the USAMRDC Broad Agency Announcement (BAA). Funded proposals that are managed by CDMRP counted in the program that provided the funding. Of the 99 applications received, CDMRP funded 33.

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.

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.

Funding Process

CDMRP is funded via annual congressional legislation known as the Defense Appropriations Act. 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.

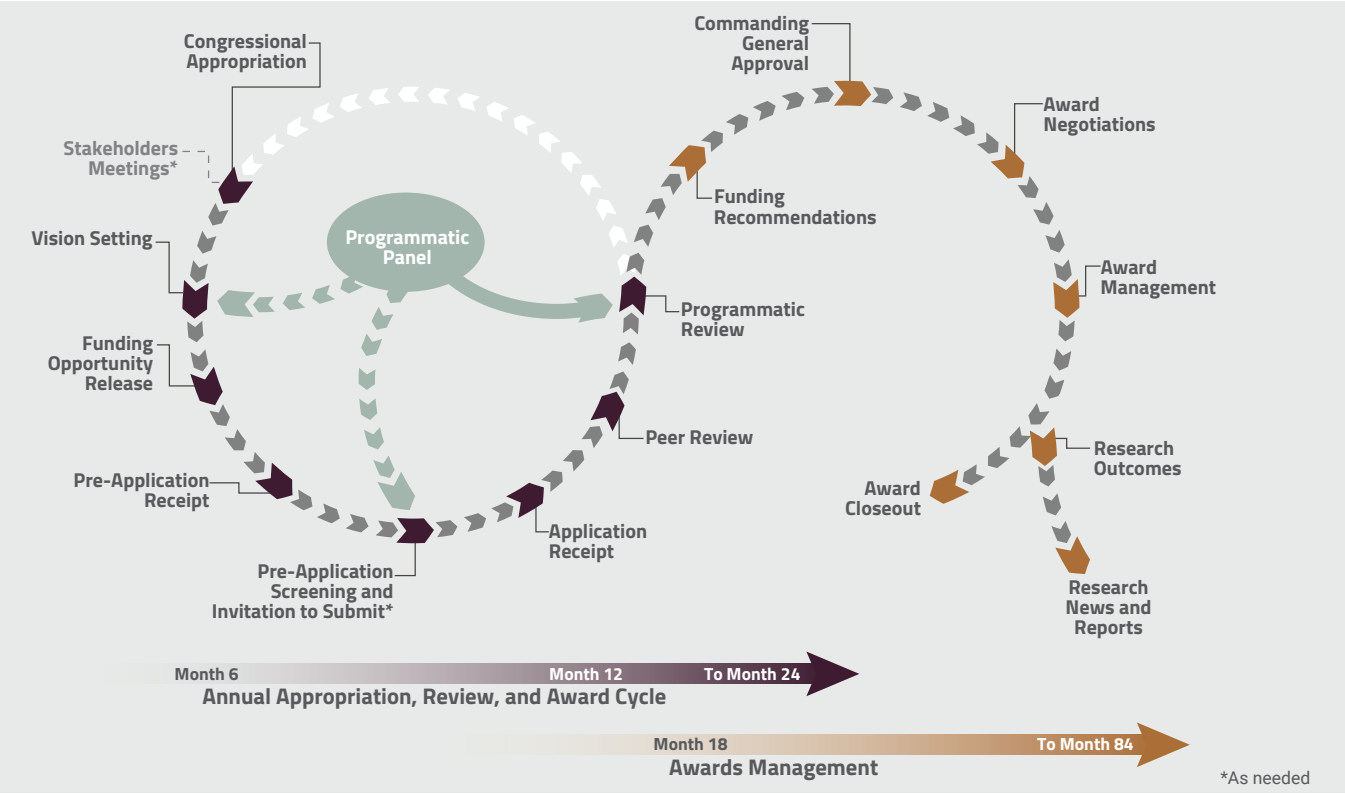


Figure 2. Program Management Cycle

1 Congressional Appropriation, Core Dollars, and Receipt of Funds

Funds for CDMRP programs have been added annually to the Defense Appropriations Bill in response to the needs of Service members, beneficiaries, research communities, consumers, and the public at large. CDMRP also provides program and award management support to the DOD for core military medical research efforts.

2 Stakeholders Meeting

A Stakeholders meeting is held at the initiation of a new program and periodically thereafter. The goal of the meeting is to bring together stakeholders to survey the research landscape and identify important gaps and opportunities for research. Stakeholders are world-renowned consumers, scientists, clinicians, and others who have an interest in any given field or topic related to the program. Recommendations from the Stakeholders meeting are used to facilitate vision setting.

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; and develop a recommended investment strategy to fill these gaps. The development of an annual investment strategy is based on the recommendations of the NAM. 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 panel's discussions, the vision setting process concludes with the development of an 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 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.

"Being a consumer reviewer for the Kidney Cancer Research Program (KCRP) is, I feel, one of the most important contributions that I can make in the effort to improve the understanding and treatment of kidney cancer. I can offer not only my experiences as a Stage IV patient for over a decade, but also my understanding of the wider kidney cancer community gained by talking with many other patients. I have learned during my Service with the KCRP and talking with prominent researchers is that we are on the threshold of an era when the research done to better understand and treat kidney cancer will lead to greatly improved outcomes for kidney cancer patients. This is very hopeful for the roughly 15,000 Stage IV kidney cancer patients diagnosed each year. The KCRP plays an essential role in bringing about the better future I envision by helping to fund the research that has already changed the grim prognosis I faced in 2007 and will bring about even greater improvements for future patients."

Gary Poteat, KCRP Consumer Reviewer

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 a scientific peer review panel, based on the requirements described in each PA or BAA. The final product of the pre-proposal screening is a list of invited applicants. As summarized in **Table 2**, in FY18, CDMRP received 7,645 pre-proposals that, after screening and invitation, resulted in 5,002 full applications received. In addition, CDMRP received 4,359 full applications from mechanisms that required a letter of intent, for a total of 9,361 full applications received in this fiscal year.

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 FY19, 226 pre-applications and 98 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, 2018-September 30, 2019, across FY18-FY19 Programs

Pre-Application Submissions	
Pre-proposals screened	7,645
Letters of intent received	2,003
Total pre-applications received	9,648
Full Application Submissions	
Full applications from invitations only	5,002
Full applications from letters of intent	4,359
Total full applications	9,361

6 Two-Tier Review Process

The two-tier review of applications is based on the recommendations set forth by the IOM committee in 1993 and affirmed in the 2016 report. The two-tier review process includes both peer review and programmatic review. 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.

7 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.

8 Award Negotiations and Management

Negotiation and management of awards are a major focus of USAMRDC offices and organizations, including CDMRP, USAMRAA, and ORP. During the period of performance (which can vary according to award type and may include extensions), CDMRP actively manages and monitors award progress. The awards management process is depicted in **Figure 3**. Over the past 5 years, an average of 906 new awards were made each fiscal year. As of September 30, 2019, CDMRP has managed 17,604 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 Principal Investigator (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. Technical analysis of the budget with respect to the scope of work to be performed is completed prior to the award being made in order to maximize savings and avoid overlap in research funding with other Federally funded projects. 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 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 including 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. At a minimum, all funded organizations are required to submit annual progress reports and quarterly financial reports. However, the progress, especially for larger complex awards, clinical trials, and consortia, may also be monitored through other means, including quarterly progress reports, external advisory boards, Government Steering Committees, site visits, teleconferences, and other meetings. Throughout the period of performance CDMRP, works with the PI and other DOD components in order to provide active management, facilitate communication, promote successful completion of awards, and accelerate translation of research outcomes where possible.

Multistep Process to Minimize Award Duplication and Overlap

9 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.

10 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, press 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/. New for this year, CDMRP released a webinar series on 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 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 85,000 unique recipients.

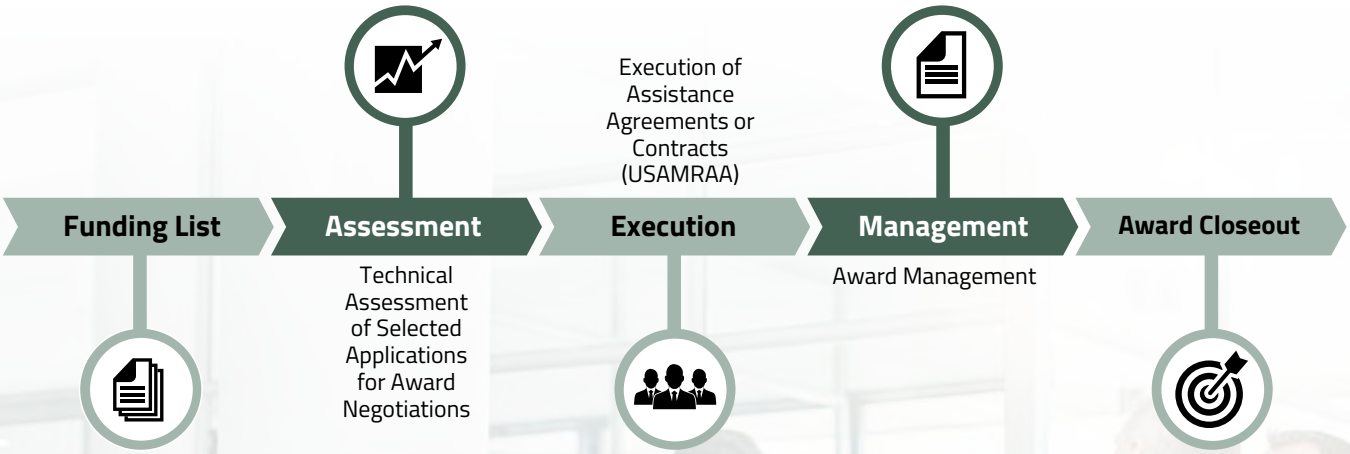


Figure 3. Awards Management Process

Vital Partnerships

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

Consumers

CDMRP promotes 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 was 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 scientific peer review panels through nominations submitted by the lay organizations. Consumers also serve at the programmatic review level of CDMRP. In each tier of review, consumers serve alongside scientists, clinicians, and leading experts, and have an equal voice and vote in deliberations.

In 2019, nearly 436 consumers served on CDMRP peer review panels and over 55 served on programmatic panels. In addition, in 2019, 15 consumers served as ad hoc reviewers on CDMRP programmatic panels. Since inception in 1992, a total of 2,686 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 research strategies and field gaps are identified during vision setting and when applications are being peer and programmatically reviewed.

In 2019, nearly 2,705 scientists and clinicians provided necessary subject matter expertise on peer review panels and over 390 scientists and clinicians served on programmatic panels. In 2019, over 225 scientists and clinicians served as ad hocs on CDMRP programmatic panels.

Since inception, approximately 12,710 researchers have been funded by CDMRP to improve the health and quality of life of all people.

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, with the responsibility for medical research, development, and acquisition management. USAMRDC is responsible for medical research programs that address both warfighters and their beneficiaries. The USAMRDC's motto, "Protect, Project, Sustain," underscores its support of the Warfighter through ensuring that solutions are provided for America's sons and daughters who serve the nation around the globe. USAMRDC's medical research programs are divided into core and non-core research programs based on their alignment with DOD and Army missions. Core programs align with the principal needs and military operations within the DOD. Non-core programs are funded through congressional additions to the Defense Appropriations Bill. CDMRP provides management support for both types of programs and works in synergy with USAMRDC partners to ensure that Defense Appropriations are used to the benefit of Service members, their families, and the American public, as shown in **Figure 4**.

Some of the research projects managed by CDMRP have the potential to become fielded products for our Warfighters. USAMRDC has designed and implemented a process called "Decision Gate" to effectively manage medical materiel development in a cost-effective, consistent, and transparent process. Decision Gate is grounded in the DOD Directive 5000 series, US Food and Drug Administration (FDA) regulations, and best industry practices, and it allows USAMRDC to remain responsive to the changing needs of the Warfighter. The ultimate goal of the Decision Gate process is to focus materiel development efforts on meeting DOD medical requirements as quickly and efficiently as possible. Projects funded through CDMRP that have strong potential for development into a beneficial, military-relevant medical product are included in the Decision Gate process. To facilitate this process, CDMRP evaluates products from its research portfolio and assigns to each a Technology Readiness Level (TRL) code. The TRL system tracks product progress from basic research and technology development through manufacturing, production, and deployment. This information is used by USAMRDC to determine whether any CDMRP-funded projects meet the criteria to be entered into the Decision Gate process, a point called the Materiel Development Decision (MDD). Once in Decision Gate, product development will be guided by an Integrated Product Team. Science Officers from CDMRP are sometimes asked to participate on the Integrated Product Teams due to their scientific expertise, history of managing relevant awards, and relationship to the product developer. As the product matures, it goes through a series of decision points (called milestones) to determine whether it should continue as planned, continue with a revised plan, or have its development terminated (see **Figure 5** for the life cycle of a medical product). There are three decision points, called Milestones A, B, and C, which roughly correspond with Phase I clinical trial, Phase II clinical trial, and FDA approval, respectively. The Decision Gate process reflects USAMRDC's commitment to remain a good steward of taxpayer dollars and a world-class medical R&D organization.

Figure 4. The USAMRDC Team

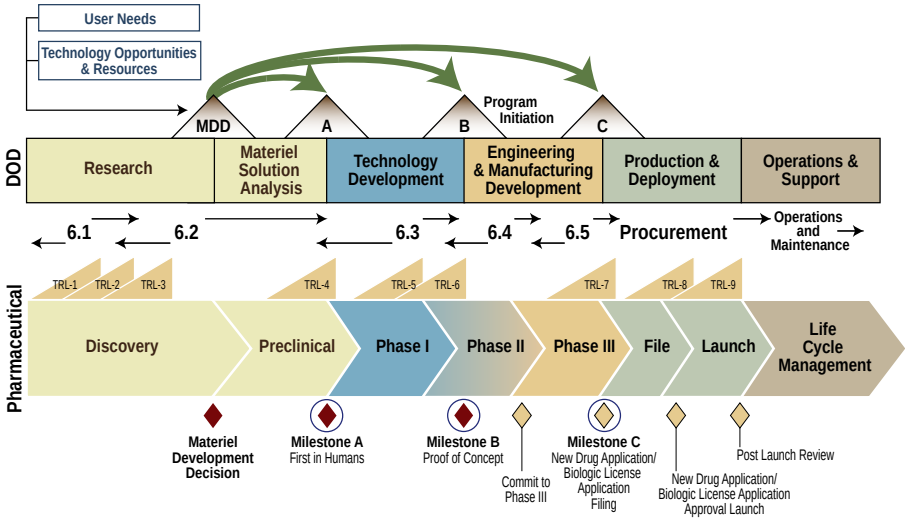


Figure 5. Decision Gate Life Cycle

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 has four goals:

- Empower and Care for Our People
- Optimize Operations across the Military Health System
- Co-Create Optimal Outcomes for Health, Well-Being and Readiness
- Deliver Solutions to Combatant Commands

The DHA J9, Research and Development Directorate, was established within DHA in 2014 as the core research program of the DOD to help coordinate and enhance the related medical R&D programs of the Army, Navy, Air Force, and Defense Advanced Research Projects Agency (DARPA). 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. DHP congressional and core programs managed or supported by CDMRP are overseen by the DHA J9, Research and Development Directorate, which works closely with CDMRP to provide:

- Centralized Oversight of R&D Grants, Projects, and Initiatives Across the Services and Military Health System to Eliminate Redundancy and Reduce Variance.
- Prioritization and Direction of Medical Research to Ensure Maximal Impact for Service members and Beneficiaries.

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, VA, NIH, and 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. While historically held only for core research and related portfolios, 18 additional CDMRP-assigned congressional programs presented at R&A meetings in FY18, and these meetings continued into FY19. This opportunity allowed participants to highlight research gaps being addressed by current programs, identify gaps requiring additional support, highlight current areas of collaborative success, identify additional opportunities for further collaboration and coordination, leverage resources, and avoid 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. There are currently six 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
- Clinical and Rehabilitative Medicine Research Program

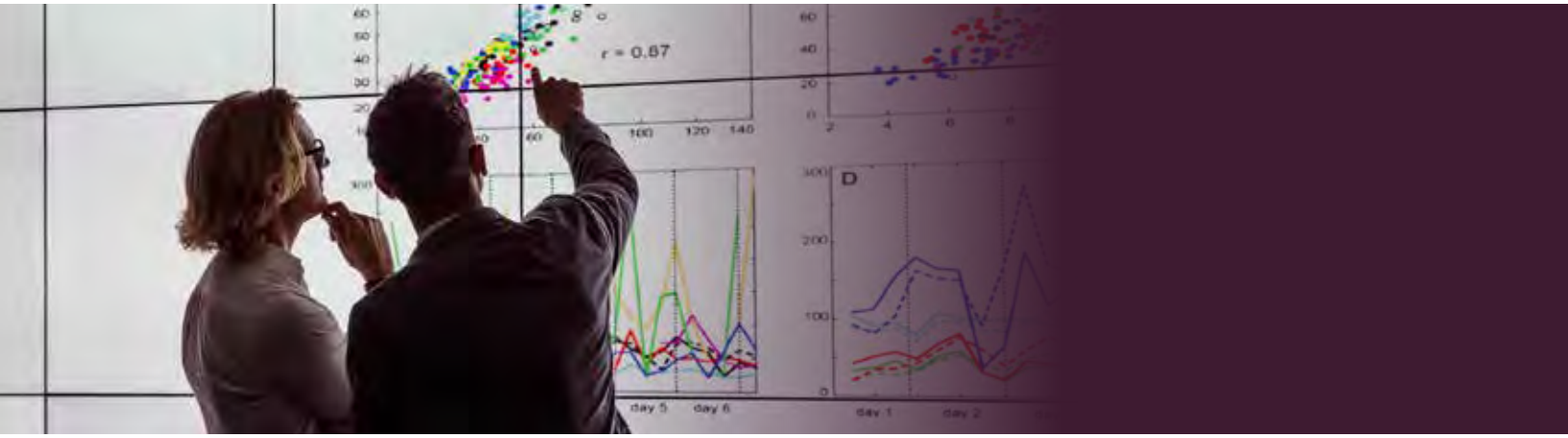
CDMRP provides award and program management support as requested to the JPCs/PADs for DHP core research program areas. The combined effort leverages CDMRP's expertise in research program administration with the PADs' technical and strategic expertise to expedite the delivery of products and solutions 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 101-111 in this report). In FY19, 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 230 investigators at VA institutions have been funded by CDMRP.

As one prime example, CDMRP's Gulf War Illness Research Program (GWIRP) is collaborating 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 52-53 for additional details on GWIRP). VA scientists and clinicians serve on both peer and programmatic review panels for GWIRP to inform and help make funding recommendations as well as to 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 $100 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 PTSD (CAP; refer to page 18) and the Chronic Effects of Neurotrauma Consortium (CENC; refer to page 17), which are described in further detail on pages 15-28 of this Annual Report.

Additionally, in 2018 and 2019, 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

Over the years, several programs led the development of research consortia and/or initiatives to build strong partnerships and collaborations within the scientific community. These multi-institutional organizations 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 (PRARP).

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 this interdisciplinary network has been focused on regenerative medicine for the treatment of severely wounded Service members. The AFIRM was initially composed of two independent civilian research consortia: the Rutgers – Cleveland Clinic Consortium and the Wake Forest – Pittsburgh Consortium, both of whom worked closely with the US Army Institute of Surgical Research (USAISR) at Fort Sam Houston, Texas. 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. The period of performance for the AFIRM ended in September 2018. In 2013, based on the AFIRM's successes, funding for the AFIRM II was made available by the same partnership of government agencies. Wake Forest was selected to lead this next phase of the AFIRM. The AFIRM II includes members from both of the initial AFIRM consortia, along with new investigators. The AFIRM II's 60 original research projects span five Focus Areas that represent critical clinical challenges needing advanced solutions for Wounded Warriors: (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 the component and 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. The AFIRM II combines the efforts of the nation's leading experts in regenerative medicine into a team whose work spans from R&D to clinical translation, implementation, and commercialization.

Bridging Advanced Developments for Exceptional Rehabilitation Consortium

BADER
BADER took a scientific approach to building the consortium. A key component was partnerships. The BADER Consortium deliberately made it easy for scientists to build meaningful partnerships.

The Bridging Advanced Developments for Exceptional Rehabilitation (BADER) Consortium, led by Dr. Steven Stanhope of the University of Delaware, supported the advancement of orthopaedic rehabilitation research capabilities at DOD Military Treatment Facilities (MTFs) and VA sites. Its overarching goal was to partner 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 8 projects, generating 43 published manuscripts, and obtained 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. The BADER Consortium activities resulted in partnerships, which have extended its initial eight funded projects. A university-MTF-VA partnership will expand research exclusively on women amputee runners; a university-VA partnership 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.

The Chronic Effects of Neurotrauma Consortium

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

CENC is a joint DOD and VA effort 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. CENC is led by PI Dr. David Cifu at Virginia Commonwealth University, with the assistance of Co-PI COL Sid Hinds at USAMRDC. Currently, over $37M has been invested in CENC, which leverages collaborations with over 30 participating institutions across academia, industry, DOD, and VA. Ten studies were initiated spanning efforts in the area of epidemiology, neurosensory co-morbidities, neuroimaging standardization, and follow-up from studies initiated in-theater. The centerpiece of the CENC is a large observational cohort study comprehensively examining 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. CENC has established a large, well-characterized, geographically dispersed study cohort that can be leveraged in other studies seeking to address mTBI in Service members and Veterans. CENC 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 http://www.cencstudy.org/.

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 almost 7,000 athletes and cadets. Almost $30M 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.

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. Eleven studies have been approved for implementation by the CAP Government Steering Committee, including two biomarker studies and three pilot projects. Two of the three pilot projects are successfully completed. Numerous VA, academic, and military institutions across the United States participate in CAP. Additional information can be found at https://tango.uthscsa.edu/consortiumtoalleviateptsd/.

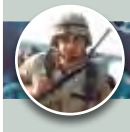
Detection of Early Lung Cancer Among Military Personnel Consortium

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 is led by Dr. Avrum Spira of Boston University, and is 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. Two projects are 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. Dr. Spira has successfully leveraged the DOD funding he received from the Lung Cancer Research Program (LCRP) to receive additional federal and industry support, with significant portions of these new investments being invested in DECAMP infrastructure. This new 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 LCRP's direct support of DECAMP came to a close in March 2019, but the significant investments from industry and other federal agencies, including independent awards managed by CDMRP, will ensure the consortium will continue 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



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

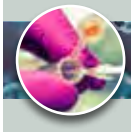
In FY18, Nova Southeastern University (NSU) was awarded a Clinical Consortium Award totaling about $6M to create a network of institutions and associated infrastructure focused on executing collaborative clinical trials, through Phase II, for the management of GWI. The Gulf War Illness Clinical Trials and Interventions Consortium (GWICTIC) aims to unify the expertise developed through past GWIRP consortium funding based at NSU and Boston University (BU) 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 (BU); 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.

Gulf War Illness Consortium

Gulf War Illness Consortium
Results from the integrated approach being utilized by the GWI Consortium should lead to a rational and efficient basis for identifying diagnostic markers and beneficial treatments for GWI.

The GWI Consortium is led by Dr. Kimberly Sullivan of Boston University. Approximately $9.5M was invested in the consortium to bring together established GWI researchers from across the nation to investigate the pathobiological mechanisms responsible for GWI symptoms as they relate to brain-immune activation and chronic inflammation. This consortium has initiated a series of clinical and preclinical studies to identify pathways that can be targeted by glial-modulating interventions and other currently available treatments. Ongoing investigations include clinical case-control studies examining markers in the blood and brain fluid, brain imaging, and memory testing. Parallel preclinical studies are evaluating persistent effects of Gulf War neurotoxicants in vitro and in rodent models of GWI. Preliminary results from the preclinical studies provide strong evidence for a neuroinflammatory component to the illness, and studies of potential treatments are currently underway in animal models. On the clinical side, preliminary results comparing cytokine, chemokine, monocyte, and lymphocytes between ill Gulf War Veteran cases and controls indicate significant differences. Brain-behavior relationships in GWI have been identified from correlations between cognitive assessment data, neuroimaging data, and cytokine profiles. The consortium has also established neuronal cell lines differentiated from Gulf War Veteran-derived induced pluripotent stem cells. In the last year of this project, researchers will validate clinical results through increased Veteran recruitment. Biospecimens and clinical data collected to date will continue to be housed in the repository now being expanded through an FY17 GWIRP award entitled, "Boston Biorepository, Recruitment, and Integrative Network (BBRAIN) for GWI." Lastly, the pilot treatment studies in the GWI model will be completed and analyzed enabling prioritization of the most promising leads.

Institute for Translational Neuroscience



ITN
Thus far, 29 unique clinical and preclinical studies have been successfully awarded and supported through the consortium. Five awards are currently active. More information regarding these studies can be found at https://itn.ucsf.edu/.

The Institute for Translational Neuroscience (ITN), headed by the University of California, San Francisco is a consortium composed of 22 institutions, that was established with congressionally directed funding in 2010 to address the growing concern regarding PTSD and alcohol and substance use disorders (ASUDs) within the military and civilian populations. Now in its seventh year of operation with funding totals close to $17M, the ITN has formed a unique and promising strategy to accelerate the development of novel therapeutics for substance use disorders and PTSD. The scientific objectives of the ITN are: (1) to identify molecular mechanisms, targets, and candidate compounds; (2) to determine the efficacy of the candidate compound(s) in vitro and in vivo (animal models); (3) to conduct proof-of-principle, pilot-scale clinical experiments or trials; and (4) to rapidly translate findings into full-scale clinical experiments/trials. To facilitate the transition from bench to bedside, the ITN established a Translational Coordinating Core to attract collaborations with outside sources, such as NIH and commercial pharmaceutical and biotechnology companies, to support follow-on clinical trials to promising ITN projects. The ITN also established an Advisory Council, consisting of members from the government, academia, and industry, to provide strategic advice, set research priorities, and serve as the primary external scientific and programmatic review for proposed research projects.

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

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

The Major Extremity Trauma Research Consortium (METRC) Coordinating Center for METRC studies is located at the Johns Hopkins Bloomberg School of Public Health. This center collaborates with four core MTFs, 22 core civilian trauma centers, and over 30 satellite centers in the US to conduct multi-center clinical studies relevant to the treatment and outcomes of orthopaedic trauma.

The METRC was initially established in 2009 with funding from the DOD and the Orthopaedic Extremity Trauma Research Program (at USAISR). In 2010, the consortium expanded in both 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, the METRC's historically acute care focus shifted to incorporate several rehabilitation Focus Areas, leading to the newly titled METRC. The PRORP has invested over $72M in METRC 2 and METRC 3 awards which provide funding support for 10 clinical studies. In addition, a number of other studies associated with METRC or using the METRC coordinating center are also being conducted. In 2017, the METRC team received funding through an FY16 Joint Warfighter Medical Research Program (JWMRP) 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. In 2018, a Clinical Practice Guideline on Management of Acute Compartment Syndrome was published by METRC in collaboration with the American Academy of Orthopaedic Surgeons.

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 and treatment 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, co-direct the consortium which has received close to $64M in funding. Consortium oversight is provided by a Military External Advisory Board, which is chaired by the Director of Military Operational Medicine Research Program.

In its initial funding period, the MSRC funded 25 studies and multiple Postdoctoral Pilot Projects and Dissertation Completion Awards and many of these studies yielded important results. In FY16, the MSRC received 5 years of additional DOD funding to continue research into expanding knowledge, understanding, and capacity to prevent and treat suicide within the military. 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 consortium currently has 24 new studies that have been funded since FY16 and are ongoing.

The MSRC has developed a database to capture Common Data Elements (CDEs) that are consistent across all projects. This database allows for secondary analysis of aggregate data across all funded studies. Additionally, the MSRC is specifically identified in The National Research Action Plan for Improving Access to Mental Health Services for Veterans, Service members, and Military Families.

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

Neurofibromatosis Clinical Trials Consortium

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

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, 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.

Ovarian Cancer Academy

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.

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 Ovarian Cancer Research Program's (OCRP) 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 FY14, Dr. Nita Maihle of Georgia Regents University and Dr. Douglas Levine, now at New York University Langone Medical Center, embraced their responsibilities as the new Dean and Assistant Dean of an expanding OCA and infused it with broader interactions between the ovarian cancer survivor and research communities. Most recently, three new FY18 ECI-mentor pairs were welcomed into the OCA, which currently brings the numbers of OCA ECIs (FY12-FY18) to 14. To date, $26M has been invested in the Academy. The OCA ECIs have demonstrated remarkable progress, resulting in 563 publications focused on ovarian and other gynecologic cancers. Their growth as independent, committed ovarian cancer researchers is evident in their 131 funded grants totaling over $50M as well as their service on the editorial boards of scientific journals and on review and panel groups for women's cancer foundations. The annual OCA in-person workshop held in Seattle in September 2018 included sessions focused on productive interactions with survivors and how to include them in the development and execution of research projects, professional development to include grants management and preparation of budgets, interactions with biotechnology companies, and how to succinctly present research results. OCA members also participated in the Marsha Rivkin Symposium, which included platform presentations from OCA members. The ECIs also took the opportunity to professionally network with the ovarian cancer team at University of Washington. The http://www.ovariancanceracademy.org/ website continues to inform the public about OCA accomplishments and has a private interactive platform that also allows the geographically dispersed ECIs and OCA leadership to collaborate effectively.

Ovarian Cancer Consortium

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

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. Their goal was to help facilitate the development of screening approaches by identifying and characterizing early changes in ovarian high-grade serous carcinomas (HGSC), the most common and malignant form of ovarian cancer.

The Ovarian Cancer Consortium completed a substantial body of work evaluating the origin of HGSC 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.

Ovarian Cancer Outcomes Consortia

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 two FY15 Outcomes Consortium Award teams led by Dr. Malcom Pike (Memorial Sloan Kettering Cancer Center) and Dr. Michael Birrer (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 to maintain focus on meaningful outcomes for ovarian cancer patients and survivors.

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. A recent publication by the team suggests that tumor infiltrating lymphocytes promote survival by a mechanism(s) unrelated to chemosensitivity. The team's preliminary data, indicates that use of both diabetes and cardiovascular medications are associated with more favorable survival.

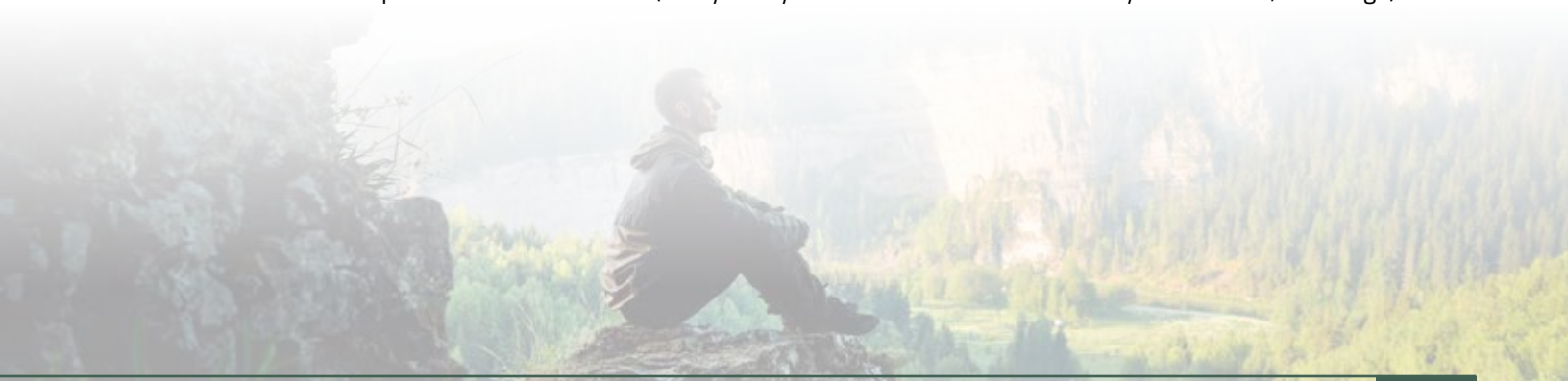
The Ovarian Cancer Consortium for the Genomic, Epigenetic, and Quality of Life Characteristics of Long-Term Survival, is focused on finding predictive biomarkers that will help in the design of individualized care for patients with ovarian cancer who were diagnosed with early-stage disease. Using data from a longitudinal analysis of quality of life from the Gynecologic Oncology Group trial-172, they developed a descriptive profile for short-, intermediate-, and long-term survivors. 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

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

Started in FY17, the Pain Management Collaboratory (PMC) Program is an interagency partnership between NIH, the DOD, and the VA. This partnership is an $81M 6-year collaborative multi-institutional research effort focused on developing, implementing, and testing cost-effective, large-scale, real-world research on non-pharmacological approaches to pain management addressing the needs of Service members and Veterans. The PMC program includes individual projects and a coordinating center, making best practices, tools, data, and other resources available to each of the projects.

The four CDMRP-managed projects being 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).



Pharmacotherapies for Alcohol and Substance Abuse Consortium

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

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. Rick Williams from RTI International, in collaboration with Baylor College of Medicine. Almost $27M has been invested in the PASA Consortium which has three aims in developing pharmacotherapies for 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. Nine active studies were funded (two pre-clinical, six clinical, and two planning grants) Clinical trials are being conducted at VA Medical Centers and MTFs.

Prostate Cancer Biorepository Network

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

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.

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.

To date about $21M has been invested in the network, and they have distributed more than 4,300 patient samples for research efforts that have resulted in 49 publications, including articles in *Nature*, *The New England Journal of Medicine*, *The Proceedings of the National Academy of Sciences*, *Cancer Research*, and *The Journal of Clinical Investigation*. Ongoing efforts to identify the most critical biospecimen needs of the research community will enable the PCBN to maintain its status as the largest, most comprehensive prostate cancer biorepository in the world designed to meet the needs of the prostate cancer research community (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 40 participating affiliate sites. In total over $57M 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. Since then, the PCCTC's extensive clinical trial experience and collaborative 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 242 clinical trials for activation, 168 of which have been completed (closed to accrual), and enroll more than 7,800 patients to these trials; 13% 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. The timing of care for these injuries has typically resembled the treatment of anterior cruciate ligament reconstruction surgery; however, there is little evidence to support this practice. 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 23 clinical sites comprised of 3 US military facilities, 17 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, in 2017. Study enrollment began in 2018; 27 patients have since been enrolled into the STaR trials.

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

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.

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 $9M, 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.

Traumatic Brain Injury Endpoints Development Initiative

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.

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 and leverages existing research infrastructure, clinical networks, and government partnerships such as the Transforming Research and Clinical Knowledge in TBI (TRACK-TBI), the Concussion Research Consortium (CRC), 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/.

Understanding Gulf War Illness: An Integrative Modeling Approach

Gulf War Illness Consortium: An Integrative Modeling Approach
Comparative analysis of cytokine expression profiles between GWI Veterans and GWI animal models paired with computer simulations has led to a Phase I study of a combination treatment in Gulf War Veterans.

Under the leadership of Drs. Mariana Morris, Nancy Klimas, and Gordon Broderick, this GWIRP-funded consortium represents expertise in neurotoxicology, animal modeling, computational modeling, and clinical research. This multidisciplinary research team, based at the Institute for Neuro Immune Medicine at NSU was awarded $9.5M and aims to develop a translational model of GWI that will identify molecular targets and predict effective therapeutic interventions while also uncovering underlying mechanisms of disease. Using computational modeling, genomic, immunological, autonomic, and endocrine pathway information from animal models of Gulf War-era chemical exposures are being integrated with observational studies of symptomatic Gulf War Veterans to discern the pathways and mediators underlying GWI. Key mediators identified from the model will then be targeted with potential therapeutic interventions. Preliminary comparative analysis of cytokine expression profiles between GWI Veterans and GWI animal models, paired with computer simulations, led to animal trials of candidate treatment protocols. Following preclinical validation, the team has moved forward with a combination treatment strategy using a tumor necrosis factor receptor antagonist, followed by a glucocorticoid receptor blockade in a Phase I study of Gulf War Veterans. The research team plans to repeat the dynamic modeling before treatment and during the trial to further inform the computation model and the impact of the intervention.

Participation in other Federal and Non-Federal Organization Efforts

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.

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:

Advisory Committee on Breast Cancer in Young Women
A Centers for Disease Control and Prevention-led body 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 ensure that no amputee feels alone through pre- and post-amputation and recovery and to 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.

Federal Interagency Health Equity Team
The mission of the Federal Interagency Health Equity Team 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 autism spectrum disorder (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 56 cancer-funding organizations that work together to enhance the impact of research to benefit all individuals affected by cancer through global collaboration and strategic coordination.

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 science and progress on funded awards.

Tuberous Sclerosis Alliance
A group dedicated to finding a cure for tuberous sclerosis complex while improving the lives of those affected.

"Metastatic breast cancer stole my career, and one day it will steal my life. But through this horrible diagnosis, I was introduced to amazing women and men who showed me that I could still help others and make a difference through advocacy. I went to conferences, I raised money for metastatic specific research, I used my voice to demand more for those of us with Stage IV, the forgotten ones in the sea of pink that surrounds breast cancer. My mantra became "Research, not Ribbons." I found out about the DOD BCRP and the role of the consumer reviewer. I applied, and was accepted, joining my first panel in January 2017. I am able to use my scientific background and medical training once again, in reading grant proposals. I have a seat at the table with brilliant scientist-reviewers, who listen to what I – and other consumer reviewers – have to say. I am useful again."

Kelly Shanahan, 2017 BCRP Consumer Reviewer

The 34 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.

Our Programs

Alcohol and Substance Abuse Disorders Research Program

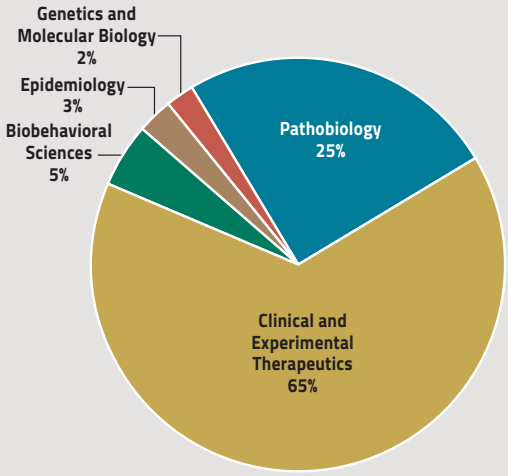
Vision: Decrease the clinical impact of alcohol and substance abuse

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

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, "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.[1] 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 from 2005-2009.[2] Furthermore ASUDs significantly worsen the hyper-arousal effects of PTSD, a disorder that affects 14% of all previously deployed US military personnel.[3] ASUDs 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 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, and federal funding for its research has led to a total appropriation of $36.075M to the ASADRP.

The goal of the program is to identify and develop new medications to improve treatment outcomes for ASUDs, especially related to TBI and PTSD. 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.



FY10-FY18 ASADRP Portfolio Investment by 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. 2013. Substance Abuse in the Military. National Institute on Drug Abuse, 1 Mar. 2013 (https://www.drugabuse.gov/publications/drugfacts/substance-abuse-in-military)

Institute of Translational Neuroscience Consortium

Sudie E. Back, PhD, Professor of Psychiatry and Behavioral Sciences at the Medical University of South Carolina and Ralph H. Johnson Veterans Affairs Medical Center

Dr. Back and her team are conducting clinical trials to examine the efficacy of N-acetylcysteine (NAC), an over-the-counter antioxidant that modulates glutamatergic functioning, in reducing symptomatology associated with alcohol use disorder (AUD) and comorbid PTSD in Veterans. The study team is utilizing a randomized, double-blind, between-groups experimental design of 8 weeks of treatment with NAC or placebo and assessing specific measures of AUD severity and PTSD symptomatology, as well as impairment in associated areas of functioning. The team is further utilizing functional magnetic resonance imaging and magnetic resonance spectroscopy to investigate potential biomarkers of treatment outcomes with NAC. The findings of this study will provide critically needed empirical evidence to help inform practice guidelines and better serve the needs of US Service members, Veterans, and their families.

Mardi M. Smith, PhD, Interim Division Officer and Clinical Psychologist at the OASIS Residential Treatment, Center at the Naval Medical Center, San Diego

Dr. Smith and her team are investigating the efficacy of intranasally administered oxytocin to decrease craving to use alcohol and other substances and stress reactivity following exposure to laboratory-induced stress among active duty military with a dual diagnosis of ASUD and PTSD. Building on previous studies in Veterans, which indicate that oxytocin can attenuate cortisol reactivity in response to a laboratory stressor in an outpatient Veteran population, Dr. Smith and her team are currently assessing these effects in an inpatient, active duty military population. If the oxytocin effects in an active duty military population proves successful, this could allow for dissemination of a safe and novel potential treatment for this targeted group of Service members.

The Pharmacotherapies for Alcohol and Substance Abuse (PASA) Consortium

Lori L. Davis, MD (left) and Ismene Petrakis, MD, (right) Kappa Opioid Receptor Antagonism for the Treatment of Alcohol Use Disorder and Comorbid PTSD, Tuscaloosa Research & Education Advancement Corporation/Tuscaloosa VA Medical Center

Dr. Davis and Dr. Petrakis are currently leading a study entitled 'Kappa Opioid Receptor Antagonism for the Treatment of Alcohol Use Disorder and Comorbid PTSD.' This Phase II Randomized Controlled Trial focuses on evaluating the efficacy and physiological effects of sublingual buprenorphine (Subutex) combined with extended-release injectable naltrexone (Vivitrol) in the treatment of comorbid AUD and PTSD. Three study sites (Tuscaloosa, West Haven, and Atlanta) will enroll a total of 135 male and female, treatment seeking Veterans and Service members with comorbid AUD and PTSD. The primary objective is to address the deficit in pharmacological treatments for comorbid AUD and PTSD and improve outcomes for patients with AUD and PTSD at 8 weeks. This trial is anticipated to last 36-months, with a 24-month enrollment period.

Colin N. Haile, MD, PhD, Anti-Fentanyl Vaccine, University of Houston

Dr. Haile's current work addresses pre-clinical research gaps in assessing potential treatments for PTSD and for those individuals that are comorbid with Opioid Use Disorder. In his second PASA-funded study, he and his team will examine a combination therapy that includes buprenorphine and an anti-fentanyl vaccine that may potentially enhance the therapeutic effect for Opioid Use Disorder. Research on potential treatments addressing the present opioid use and opioid-associated death crisis in the United States is of extreme priority. Present treatments have not proven effective, and novel treatment options are needed.

[3] Acosta JD, Martin LT, Fisher MP, et al. 2012. Assessment of the Content, Design, and Dissemination of the Real Warriors Campaign. (https://www.rand.org/content/dam/rand/pubs/technical_reports/2012/RAND_TR1176.pdf; https://www.rand.org/pubs/technical_reports/TR1176.html)

[4] Jacobsen LK, Southwick SM, and Kosten TR. 2001. Substance use disorders in patients with post-traumatic 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. doi:10.1016/j.neuropharm.2011.04.032 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3166556/)

[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

Amyotrophic Lateral Sclerosis Research Program

Vision: Improve treatment and find a cure for ALS

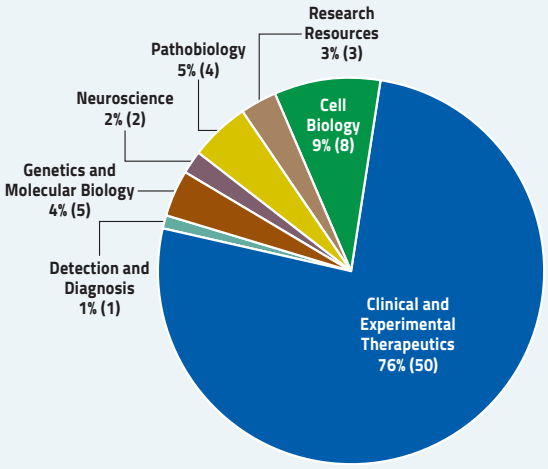
Mission: Fund innovative preclinical research to develop new treatments for ALS for the benefit of Service members, Veterans, and the general public

Program History

The Amyotrophic Lateral Sclerosis Research Program (ALSRP) was created in 2007 when the DOD redirected $5M of Army RDT&E 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). From the inception of the program, 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. The ALSRP's Programmatic Panel includes program directors from other federal funding agencies, such as the NIH and the VA. These panel members provide information regarding the research being funded by their organizations in related areas to ensure synergy and prioritization of the most promising leads.

"The NIH and ALSRP share a strong commitment to finding effective treatments for ALS. To reach this goal, NIH supports a broad range of activities from basic ALS research to clinical studies in people with ALS. ALSRP's focus on preclinical therapy development complements the ALS programs of NIH and both funders work synergistically to move ALS research forward."

Amelie Gubitz, ALSRP Programmatic Panel Member
Program Director for Neurodegenerative Cluster, NIH
National Institute of Neurological Disorders and Stroke



FY07-FY18 ALSRP Portfolio Investment by SCS Code (Number of Awards)

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 NAM (formally the IOM), 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.

Program Portfolio

The ALSRP maintains a bridge through which discoveries in the laboratory can lead to advanced therapeutic development and clinical trials. The ALSRP has focused on awards that support preclinical development of therapeutics. Areas of emphasis include development and/or validation of high-throughput screens to exploit novel targets with therapeutic potential and development of candidate therapeutics agents through the many steps required before FDA approval as an investigational new drug.

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

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

Research Highlight

ALS Treatment, AT-1501, Enters Clinical Trial

Steven Perrin, PhD, ALS Therapy Development Institute

ALSRP investigator, Dr. Steve Perrin, Chief Executive Officer of the ALS Therapy Development Institute, had previously utilized ALS mouse models to evaluate treatments that targeted the protein, CD40 Ligand. Dr. Perrin's group had correctly predicted that blocking CD40 Ligand would slow progression of ALS by preventing the activation of a pro-inflammatory immune response. This finding led to Dr. Perrin's FY16 ALSRP Therapeutic Development Award to assess the pharmacokinetics and toxicology of a new ALS antibody therapeutic, AT-1501, designed to block CDL40 activity in non-human primates. In this preclinical trial, AT-1501 successfully prevented the molecular signaling that normally activates an inflammatory response in ALS. Furthermore, AT-1501 did not cause harmful clotting, which had been a problem with other CDL40-blocking drugs.

In response to the successful outcomes of Dr. Perrin's FY16 ALSRP award, as well as further development efforts by ALS Therapy Development Institute, the FDA granted Orphan Drug Designation and Investigational New Drug approval of AT-1501 in April 2018. In addition, Anelexis Therapeutics, LLC, provided funding for a Phase I clinical trial to determine the safety of AT-1501 as an ALS treatment strategy and to analyze the drug's pharmacokinetics. This trial is ongoing and is enrolling eight individuals with ALS in addition to healthy controls. According to Dr. Perrin, seeing a lead candidate from his research team reach people with ALS is a good sign that we are moving closer to ensuring patients living with ALS can get the treatment they need.

ALSRP Consumer Reviewer: Matt Bellina had been a naval aviator, flying the EA-6B Prowler out of Naval Air Station Whidbey Island on Washington's Puget Sound when the twitching and loss of coordination began. By the time he was given a preliminary diagnosis of ALS, Matt had already been grounded due to his worsening symptoms. The diagnosis was confirmed a little over a year later when Matt was only 30 years old. Matt found the opportunity to serve as a peer reviewer for the CDMRP ALSRP and welcomed the prospect of immersing himself further in therapeutic development efforts.

Autism Research Program

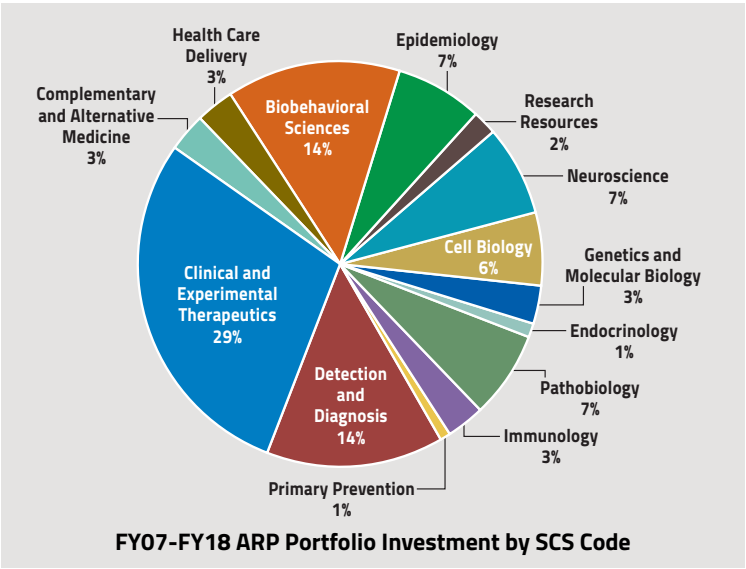
Vision: Improve the lives of individuals with autism spectrum disorders now

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

Through the program's areas of interest, the ARP focuses on ways to improve diagnosis, treatment, and studying psychosocial factors for affecting key life time transitions to independence and a better life for those with autism and their families.

It was an awesome experience to be a part of the ARP Peer Review. Being a first time participant, I was not sure what to expect, but the team made the experience quite enjoyable. I loved networking with experts in different fields, with different perspectives, but, all on one accord passionately speaking and working towards the same goal of how to better service the autism community. It was unforgettable.

Dana Bryant, ARP Consumer Peer Reviewer, FY18



FY07-FY18 ARP Portfolio Investment by SCS Code

Program History

Since its inception in FY07 through FY19, appropriations totaling $89.4M have been directed to the Autism Research Program (ARP) to promote innovative research that advances the understanding of 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. 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 and are only now being brought to the forefront of the research landscape. The causes of ASD are unknown; however, progress is being made on several fronts, and the answers will likely be multifaceted. ARP focuses on funding innovative and highly impactful research while trying to complement other funding agencies' initiatives. The population of ASD individuals entering adulthood is growing, and ARP recognizes the critical need for supporting and treating adults with ASD. Recently, ARP has placed 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. Recent progress by investigators funded by ARP shows promise in the areas of (1) recognizing ASD early so that interventions may be initiated at an earlier life stage to make a difference; (2) understanding the gut-brain interactions and how to alleviate GI issues that may cause atypical developmental behaviors; and (3) understanding the needs of adult individuals with ASD.


Facilitating the Transition to Employment for Young Adult Military Dependents with Autism Spectrum Disorder

Paul Wehman, PhD (left) and Carol Schall, PhD (right), Virginia Commonwealth University

Young adults living with ASD often experience challenges with their transition from high school to employment, as well as higher rates of unemployment and underemployment compared to those with other disabilities. The risk for poor outcomes may be even greater for military dependents with ASD, as they are subject to frequent relocation and lack consistent access to support programs that assist with the transition to employment. With support from an FY15 ARP Clinical Trial Award, Drs. Paul Wehman and Carol Schall are assessing the effectiveness of Project SEARCH, a 9-month employment-based training program for improving social communication, behavior, and employment outcomes for transition-aged youth with ASD. Project SEARCH allows young adults with ASD who are in their last year of high school to be immersed in large community businesses with real-world work environments such as hospitals, government complexes, or banking centers and rotate through three 10- to 12-week internships and complete 900 classroom and internship hours learning marketable skills. To meet the unique needs of military dependents with ASD, the Project SEARCH model was enhanced through the addition of Autism Supports, yielding Project SEARCH Plus ASD Supports (PS+ASD). The modified PS+ASD program provides an opportunity for military youth to learn job skills at their current installation that can be generalized to new installations in the event of a relocation. PS+ASD consists of intensive applied behavioral analysis, support from an on-site behavior and autism specialist, and staff training in ASD and the Project SEARCH model. Participation in the Project SEARCH model has been shown to improve independence, social responsiveness, self-management, work skills, and quality of life. The PS+ASD model has been implemented at a site at Fort Eustis at Joint Base Langley-Eustis in Virginia. The first cohort of the program has graduated, and 83% have accepted competitive employment offers. This interventional PS+ASD model provides the necessary elements for a seamless and successful transition from school to employment for military dependents with ASD. Dr. Wehman's research has the potential to not only contribute to research and clinical practice, but also to meet the needs of military dependents with ASD by increasing employment opportunities and enhancing social communication. If successful, this work will support professionals and military personnel by identifying viable treatment models in the transition to employment for military dependent youth with ASD.



Treating Gastrointestinal and Autism Symptoms in Adults with Autism Using Microbiota Transfer Therapy

James Adams, PhD (left), and Rosa Krajmalnik-Brown (middle), Arizona State University

Richard Frye, MD, PhD (right), Phoenix Children's Hospital

Individuals with ASD frequently suffer from constipation, diarrhea, and other GI problems that are resistant to treatment and could last for several years and even decades. These GI problems are often painful, produce anxiety, and severely affect quality of life. With support from an FY15 ARP Clinical Trial Award, Drs. James Adams, Rosa Krajmalnik-Brown, and Richard Frye sought to evaluate the efficacy of Microbiota Transfer Therapy (MTT) in adults with ASD who have GI problems and assess the potential role of gut bacteria on both GI and ASD symptoms. MTT involves administration of vancomycin (an antibiotic) to clean the gut and reduce pathogenic bacteria, followed by administration of a standardized human gut microbiota preparation to restore healthy gut microbiota. A previous pilot study completed by Dr. Adams, Krajmlanik-Brown, and collaborators in which MTT was administered to 18 subjects with ASD and GI problems demonstrated an 80% reduction in GI symptoms, as well as significant improvements in ASD symptoms. The current trial is a randomized, double-blind, placebo-controlled study of MTT in 84 adults with ASD and includes a widespread evaluation of GI and ASD-related symptoms and microbiome composition, blood safety examinations, and 6-, 12-, and 18-month follow-ups. To date, the trial has 29 participants enrolled, 18 of which have completed treatment. This trial provides a critical step in future FDA approval for MTT treatment in individuals with ASD. If successful, this work is expected to help approximately 40% of individuals with ASD who suffer from chronic GI problems, significantly reduce their ASD symptoms, and improve their quality of life.

Bone Marrow Failure Research Program

Vision: To understand and cure bone marrow failure diseases

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

Program History

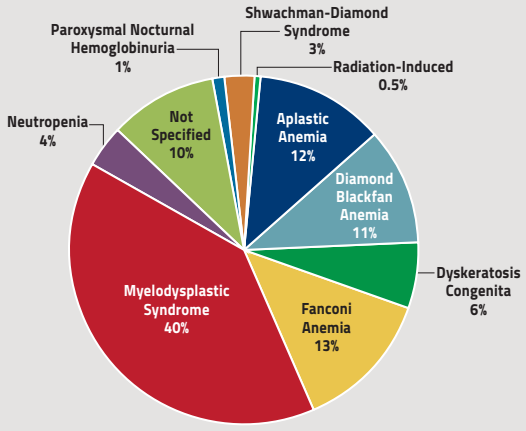
The cavities of bones are made up of a spongy tissue that contains stem cells capable of maturing to blood cells in a process known as hematopoiesis. The hematopoietic cascade is responsible for the development of all cellular blood components, including red blood cells, white blood cells, and platelets. 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 in which somatic genetic mutations lead to a deficiency in hematopoiesis that presents itself in childhood or early adulthood. Acquired BMF includes a group of diseases that can occur following an environmental exposure such as ionizing radiation, chemical contamination, or the long-term effects of chemotherapeutics. Both types of BMF lead to life-long chronic illnesses with the potential to develop cancer. The Bone Marrow Failure Research Program (BMFRP) was initiated in FY08 to provide support for exceptional innovative research focused on BMF diseases. From FY08 through FY18, $35.55M has been appropriated by Congress to research the prevention, causes, and treatment of BMF diseases. The appropriation for FY19 for the BMFRP is $3M. Thus far, the BMFRP has funded 71 awards, with the mission to support innovative research committed to advancing the understanding of inherited and acquired BMF diseases.

Examples of *inherited* BMF

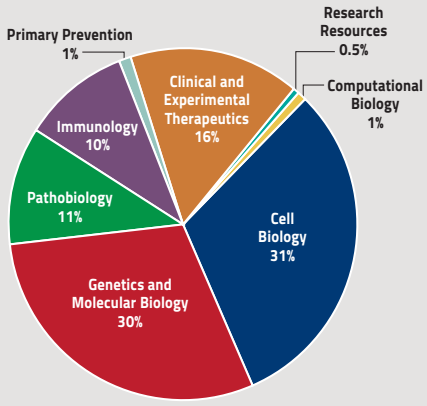
- Fanconi anemia
- Dyskeratosis congenital
- Shwachman-Diamond syndrome
- Diamond-Blackfan anemia
- Inherited neutropenia

Examples of *acquired* BMF

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



FY08-FY18 BMFRP Portfolio Investment by Disease Classification



FY08-FY18 BMFRP Portfolio Investment by SCS Code

*Percent Dollars Invested

A Method for Rescuing Hematopoietic Stem Cell Functions in Fanconi Anemia

Wei Tong, PhD, Children's Hospital of Philadelphia

Fanconi anemia (FA) is a rare and fatal inherited blood disorder caused by a mutation in one of 22 FA genes. These genes promote stable hematopoietic stem cell (HSC) development which becomes diminished when FA occurs, leading to severe BMF, leukemia, and loss of life. Stem cell transplant remains a standard course of treatment but comes with associated risks. Dr. Wei Tong discovered a gene, LNK (also called SH2B3), which, when disrupted, leads to the expansion of HSCs in both healthy and FA animal models. Through a FY16 Bone Marrow Failure Research Project Idea Development Award, her team sought to determine the role of LNK mechanism in the maintenance of HSCs. They determined that the mechanism for restored HSC activity was through the JAK pathway, a pathway known for promoting blood formation and immune response. The work was done in mouse models of FA and the intended next research steps are to study LNK mechanism for HSC restoration in human FA patients. Dr. Tong's work represents the first published incident of an investigator successfully reversing FA-associated HSC defects and successfully restoring function and genomic stability to HSC progenitor cells in FA-associated animal models to healthy levels. This line of research offers new targets and treatment strategies for FA and other BMF diseases. It has uncovered a possible means of restoring function in HSCs without stem cell transplants, thus avoiding the high risks of morbidity and mortality associated with that treatment.

Replicating the Patient-Specific Bone Marrow Failure Disease in Order to Identify Therapeutic Response

Benjamin Ebert, PhD, Brigham and Women's Hospital

Myelodysplastic syndromes (MDSs) are the most common cause of acquired BMF in the United States. A current form of therapy involves hypomethylating agents, but patients have varying responses to the agents. Dr. Ebert hypothesized that patient-specific mutations alter the response to the therapy, and with support from an FY13 BMFRP award he set out to identify mutations that will predict response to hypomethylating therapy. MDS-treated patient samples were screened, and mutations were identified that predicted response to hypomethylating agents. In order to confirm that these mutations reflect patient sensitivity, Dr. Ebert's team developed models of human bone marrow diseases that reflect the complexity of genetic mutations. This was accomplished by simultaneously modifying the disease driver genes, along with multiple other genes in human HSCs, and then permitting their expansion in a mouse model. The team determined that mutations in TET2 and in the cohesion protein subunits increased the sensitivity of human HSCs to hypomethylating agents, while ASXL1 mutations decreased the sensitivity. Dr. Ebert's results not only indicate which MDS patients would most benefit from treatment with hypomethylating agents, but they also highlight a model system for precision medicine that could have immediate clinical impact. With Dr. Ebert's model system, researchers are able to mimic the genetic complexity of BMF, which could then facilitate pharmacologic testing in a patient-specific fashion.

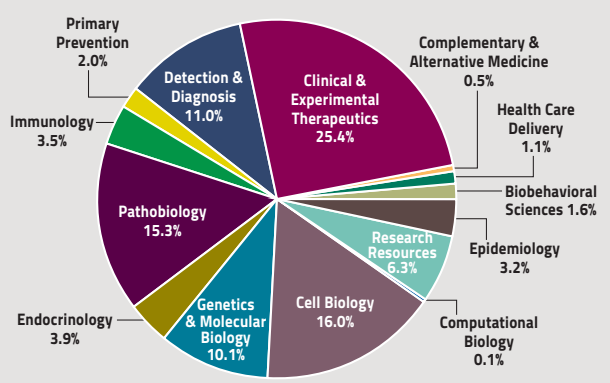
"In 2003, my family's life changed forever. Our 21 year old son, Jake, was diagnosed with FA. To say we were stunned is an understatement. He needed a bone marrow transplant immediately. We were ecstatic when we found that our youngest son Spencer was a perfect match. As he was being tested to be Jake's donor, it was discovered that Spencer had the same disease. Now not only did Jake not have a sibling matched donor, Spencer would be battling the same devastating thing. Jake tragically passed away from complications of his transplant eight months after being diagnosed. Thankfully, Spencer is stable at this time. Since Jake passed away, I have gotten over a thousand people on the bone marrow registry and raised over a million dollars for FA research. Research is our hope and it has become my passion in life. This was my third year participating as a consumer peer reviewer for the BMFRP. I am very interested in BMF research and am happy to do something that could benefit not only those with FA, but those with other BMF diseases as well."

Peggy Padden, FY15, FY18, BMFRP Peer Reviewer

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



FY92-FY18 BCRP Portfolio Investment by SCS code

Program History

The DOD Breast Cancer Research Program (BCRP) plays a leading role in the fight against breast cancer through its innovative approaches and its focus on research that addresses the overarching challenges to bring an end to this disease. The BCRP was established in 1992 and has received annual appropriations totaling over $3.6B through FY19 as a result of the dedicated efforts of breast cancer advocates. 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.

Relevance to Military Health

Breast cancer is the most common non-skin cancer in women, causing the most cancer-related deaths in women under the age of 40.[1] Female active duty Service members have a 20%-40% higher incidence rate of breast cancer than the general public.[2] The incident rate of breast cancer for active duty women is seven times higher than the average incident rate of fifteen other cancer types across all Service members.[3] The outcomes of BCRP-funded research will ultimately benefit military Service members, Veterans, military beneficiaries, and the general public.

Overarching Challenges

The BCRP recognizes that many overarching questions still remain unanswered in breast cancer, and funding must be invested in critical areas of research in order to make breakthroughs that will save lives and lead to the eradication of this disease. To meet this urgent need, the FY19 BCRP requires all applications to address at least one of the following overarching challenges within the Breast Cancer Landscape:

- 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

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

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

[3] Lee T, Williams V, Taubman S, and Clark L. 2016. Incident diagnoses of cancers in the active component and cancer-related deaths in the active and reserve components, U. S. Armed Forces, 2005-2014. *Medical Surveillance Monthly Report* 237: 23-31.

New Clinical Trials in 2019

Denosumab (XGEVA®); Phase III (EudraCT Number: 2017-002505-35)

Josef Penninger, PhD, Institute of Molecular Biology, Vienna, Austria

This Phase III clinical trial, which resulted from Dr. Penninger's findings, will determine whether prophylactic administration of denosumab in BRCA1 mutation carrier women can prevent breast cancer. A new FY18 BCRP award led by Dr. Judy Garber and Dr. Christian Singer will expand this effort through a second Phase III clinical trial comprised of over 60 anticipated clinical sites.

HER2 Peptide Vaccine (H2NVAC); Phase Ib (NCT03793829)

Keith Knutson, PhD (pictured left), Mayo Clinic Jacksonville; Amy Degnim, MD (pictured right), Mayo Clinic Minnesota

H2NVAC is currently in a Phase I clinical trial (NCT01632332) and has been shown to be well tolerated by patients. This BCRP-funded Phase Ib clinical trial, which will expand on the Phase I trial, includes a dose escalation phase to determine the optimal dose and safety of H2NVAC when administered in the neoadjuvant setting in patients with ductal carcinoma in situ. In addition, the Phase Ib clinical trial will determine whether the vaccine can induce persistent immunity against breast tumors expressing HER2 and, ultimately, help to provide protection against recurrence. The trial is open and actively accruing.

Breakthroughs in Understanding the Tumor Immune Microenvironment

Sensitizing Metastatic Breast Cancer to Immune Checkpoint Blockade (ICB) Therapy

Rakesh Jain, PhD, Massachusetts General Hospital

An immunosuppressive tumor microenvironment renders ICB therapy ineffective in metastatic breast cancer patients. Research supported by the BCRP showed that CXCR4, a chemokine receptor known to be associated with immunosuppression, was upregulated in both metastatic and primary tumors and correlated with a shorter progression-free survival. In mouse models with established metastatic tumors, median survival was significantly extended when Plerixafor, an FDA-approved CXCR4 inhibitor, was given in combination with ICB therapy. Moreover, in TNBC tumor-bearing animals, 57% of combination therapy treated animals remained disease-free for more than 6 months after treatment initiation.

Chen IX, Chauhan VP, Posada J, et al. 2019. Blocking CXCR4 alleviates desmoplasia, increases T-lymphocyte infiltration, and improves immunotherapy in metastatic breast cancer. *PNAS* 116(10):4558-4566.

Reprogramming the Pro-Tumorigenic Immune Microenvironment

Lalita A. Shevde, PhD, University of Alabama at Birmingham

Tumor-associated macrophages have been shown to be highly flexible, with the capability of polarizing into either M2 (tumor-promoting) or M1 (tumor-killing). With BCRP support, Dr. Shevde used in vitro models to demonstrate that tumor-derived hedgehog (Hh) signaling activates M2 polarization through an upregulation of Hh signaling within the macrophages themselves. Tumor-bearing mice treated with the FDA-approved Hh inhibitor, Vismodegib, had a significant increase in the number of tumor-associated M1 macrophages within the tumors and a significant reduction in the number of lung metastases.

Hanna A, Metge BJ, Bailey SK, et al. 2018. Inhibition of hedgehog signaling reprograms the dysfunctional immune microenvironment in breast cancer. *Oncoimmunology* 8(3): 1548241.

Neutrophil Extracellular Traps (NETs) Awaken Dormant Disseminated Tumor Cells (DTCs)

Mikala Egeblad, PhD, Cold Spring Harbor Laboratory

Neutrophils are key inflammatory response cells that release NETs, which are mixtures of DNA and enzymes that can modify laminin in the extracellular matrix, resulting in the reawakening of dormant DTCs and an increase in metastases. Dr. Egeblad's team generated an antibody, Ab28, and showed that Ab28 bound laminin only after it had been modified by chronic inflammation and was in close proximity to NETs and proliferating cancer cells. Moreover, a version of Ab28 with low immunogenic potential was able to block inflammation-induced awakening of dormant DTCs in the lung.

Albrengues J, Shields MA, Ng D, et al. 2018. Neutrophil extracellular traps produced during inflammation awaken dormant cancer cells in mice. *Science* 361(6409).

Breast Cancer Research Semipostal Program

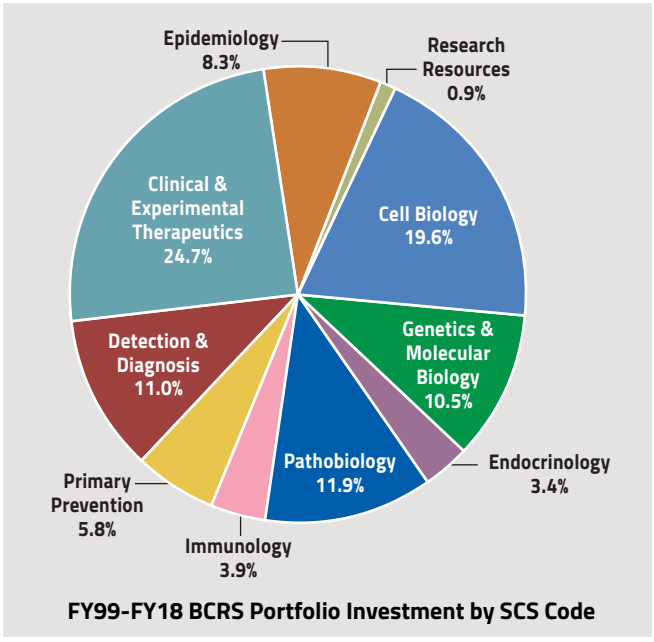
Program History

As a result of the efforts of BC advocates, 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 2015 reauthorized the stamp through 2019.

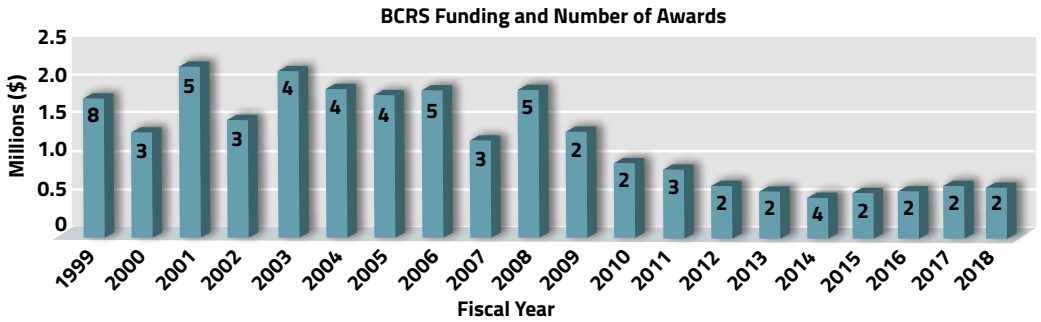
Research and Management Costs

Breast cancer stamp funding received by the BCRP between FY99 and FY18 has been used to fully or partially fund 67 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.

Total Proceeds from BCRS (through FY18)	$25,858,015
Research	$24,606,277
Management Costs	$1,251,738



FY99-FY18 BCRS Portfolio Investment by SCS Code



Damaged Progenitors as Targets for Breast Cancer Prevention

Leif Ellisen, MD, PhD, Massachusetts General Hospital

The cell-of-origin in breast cancer gene 2 (BRCA2)-associated breast cancers is thought to be a luminal progenitor (LP) cell, and inherited mutations in the BRCA2 gene are correlated with an increased risk of developing breast cancer. Dr. Ellisen and his team discovered a subpopulation of DNA-damaged LP cells representing the earliest pre-cancerous precursors in BRCA2-mutation carrier women. Dr. Ellisen first noted an increase in the proportion of LP cells in healthy breast tissue from BRCA2-mutation carriers that also correlated with increased age, such that older women had a higher proportion of LP cells in their breast tissue compared to younger women. In addition, of the entire population of LP cells in the breast tissue of BRCA2 carriers, a significant number of cells exhibited gains and losses of portions of multiple chromosomes. Further analysis of BRCA2-mutant LP cells revealed a gene expression signature that was consistent with failed activation of cell division checkpoints and suppression of DNA damage-induced signaling of nuclear factor kappa B (NFκB), a transcription factor that plays a critical role in the cellular response to stress and DNA damage. Because deregulation of cell growth by cell cycle stress is correlated with malignant transformation, and suppression of NFκB signaling pathways is associated with increased genomic instability, these findings suggest that early DNA damage precedes visible cellular abnormalities in the BRCA2 cancer-predisposed breast. These results provide proof-of-principle for exploiting the abnormal DNA damage and cell cycle checkpoint phenotype as a potential cancer prevention strategy for high-risk BRCA2-mutation carrier women. Dr. Ellisen received follow-on funding with an FY18 BCRP Expansion Award to continue his work to identify novel pharmacologic interventions for preventing the development of breast cancer in BRCA2-mutation carriers.

Tousled-Like Kinase 2 (TLK2) Is a Potential Therapeutic Target for More Aggressive Form of Luminal Breast Cancer

Xiaosong Wang, MD, PhD, University of Pittsburgh

The luminal B subtype of estrogen receptor positive (ER+) breast cancer is more aggressive than luminal A and is characterized by poorer tumor grade, larger tumor size, a higher proliferation index, and an increased tendency to develop endocrine resistance. As reported in *Nature Communications*, Dr. Wang and colleagues developed a genome-wide analysis, ConSig-Amp, that helps to identify potential therapeutic targets in cancer from multi-genomic data sets. Using ConSig-Amp, amplification and overexpression of the TLK2 were found to be highest in the luminal B subtype of breast cancer. In addition, increased expression of TLK2 in tumor samples from breast cancer patients correlated to an overall worse clinical outcome independent of treatment with endocrine therapy. Overexpression of TLK2 in benign breast epithelial cells and TLK2-low luminal breast cancer cells increased cell migration and invasion, while inhibition of TLK2 alone or in combination with tamoxifen resulted in a significant reduction in tumor growth and increased progression-free survival in a mouse model of breast cancer. Dr. Wang and colleagues also showed that TLK2 inhibition prevents cell cycle progression and induces apoptosis in ER+ breast cancer cell lines with high expression of TLK2. Furthermore, the research team identified two potential TLK2 inhibitors, Go6983 and GF109203X, which could be used to develop future therapeutic agents to treat aggressive ER+ breast cancers that overexpress TLK2.

Kim JA, Tan Y, Wang X, et al. 2016. Comprehensive functional analysis of the tousled-like kinase 2 frequently amplified in aggressive luminal breast cancers. *Nature Communications* 7:12991.

Chronic Pain Management Research Program

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

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

Program History

The Chronic Pain Management Research Program (CPMRP) was established in FY19 with a congressional appropriation of $10M. Prior to this appropriation, 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 (including these topic areas: Acupuncture, Chronic Migraine and Post-Traumatic Headache, Chronic Pain and Fatigue Research, Chronic Pain Management, Drug Abuse, Fibromyalgia, Integrative Medicine, Interstitial Cystitis, and Non-Opioid Pain Management), 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.

"I am a person who lives with pain, but I am humbled by the men and women who serve our country; their stamina, bravery, and willingness to hold on despite so much pain. It is an honor to help shape this program. To improve understanding of pain. To explore better ways to assess and treat pain through the integrative approach looking at all modalities that comprise balanced pain management."

Penney Cowan, CPMRP Programmatic Panel Member and Consumer; Founder & CEO, American Chronic Pain Association

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 the CPMRP at its inaugural Stakeholders meeting to determine its role in chronic pain management research.

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, whom carefully considered the outcomes of the Stakeholders meeting to craft the Vision and Mission statements during the inaugural CPMRP Vision Setting. During Vision Setting, the panel members also distilled the research priorities identified at the Stakeholders meeting into Focus Areas, which will be used in PAs 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.

FY19 Focus Areas

Focus Area	Specific Knowledge Gap
Implementation Science (of evidence-based, efficacious interventions)	▪ Unique barriers in military populations and environments, including at-risk sub-populations ▪ Self-management and service of care models
Comparative Effectiveness	▪ Multimodal and combination therapies ▪ Pain and its co-morbidities ▪ Incorporation of a biopsychosocial model of assessment that includes pain interference in emotional and physical functioning
"Chronification" of Pain	▪ Understanding mechanisms and developing models for studying the transition from acute to chronic pain following trauma either physical or psychological ▪ Development of therapies to prevent and treat chronification ▪ Identification of risk factors or biomarkers for patients at risk of chronification including at-risk sub-populations

FY19 Award Mechanisms

Translational Research Award

The FY19 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, and/or practice guidelines. 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 FY19 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 in the Focus Area of Chronification of Pain. Multidisciplinary collaborations and innovative approaches are highly encouraged to gain knowledge about the transition of acute to chronic pain for development of treatments and/or preventative care.

For all FY19 CPMRP award mechanisms, the incorporation of pain informatics, pragmatic approaches, and patient expectations, preference, and goals of treatment at point of care in research approaches is encouraged.

"I was delighted that the CPMRP is being developed as one of the Congressionally Directed Medical Research Programs. It was such a privilege and honor to participate in the Stakeholders meeting to set priorities of the pain research needs in the military, representing the Cleveland Clinic and the American Academy of Pain Medicine. As our nation and Servicemen and women face the challenges of dual crises of chronic pain and the opioid epidemic, this new timely program is an integral part of our national efforts to find new solutions to combat these critical problems."

Jianguo Cheng, MD, PhD, FIPP, CPMRP Stakeholder; Immediate Past President, American Academy of Pain Medicine; Professor of Anesthesiology, Departments of Pain Management and Neurosciences, Cleveland Clinic Foundation

Clinical Research Intramural Initiative

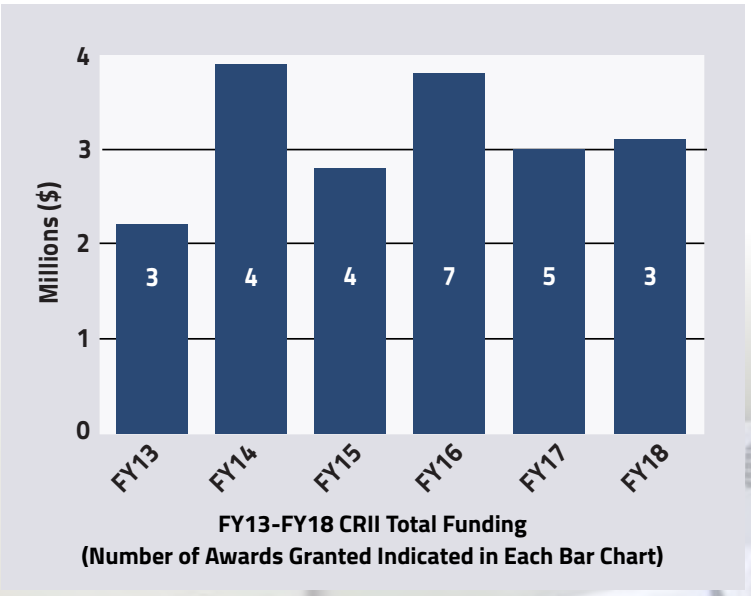
Mission: To promote and support biomedical research at Military Treatment Facilities (MTFs) for the benefit of the Service member, Veterans and beneficiaries

Program History

The Clinical Research Intramural Initiative (CRII) was established in 2012 to provide support for intramural clinical research in 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 on military personnel, families, and communities while supporting the development of military researchers and building Military Health System 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 26 awards through FY18 totaling approximately $18.8M to funds efforts in Intramural initiated Research, Military Training Injuries, Health Services, Precision Medicine, Military Women's Health and Military Performance Optimization.



FY13-FY18 CRII Total Funding
(Number of Awards Granted Indicated in Each Bar Chart)

Clinicians and Scientists at Uniformed Services University Develop Clinical Decision Support Tools for Predicting Health Outcomes for Patients with Advanced Prostate Cancer

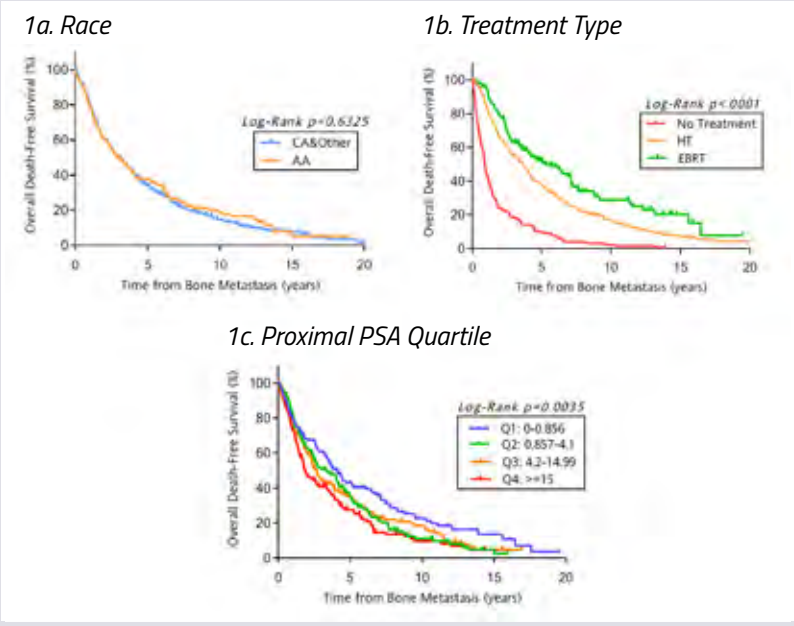
CAPT Jonathan Forsberg, MD, PhD, Uniformed Services University-Walter Reed National Military Medical Center

Dr. Jennifer Cullen, PhD, MPH, Uniformed Services University

When patients progress to advanced stages of cancer, treatment and medical decisions can range from palliative care to aggressive surgery. Often the decision about which type of care to recommend is influenced by how long the patient is expected to survive. Adding to the complexity, there is great diversity in survival expectancy for different types of cancer. Given the breadth of care options and survival expectancies, it is imperative to develop informative clinical support tools to determine the optimal care plans for patients. Seeking to standardize the manner in which physicians calculate patient survival, CAPT Forsberg and his team previously validated a clinical decision support tool, PATHFx, to derive objective survival estimates in patients with all types of advanced cancer. PATHFx is a clinical decision support tool supported by an international collaboration designed to improve the lives of patients living with metastatic bone disease. Developing disease-specific models may improve the physicians' ability to estimate longevity, as well as determine which patients are at risk for disease progression and skeletal-related events defined as bone pain and/or fracture due to metastatic cancer.

With support from the CRII Award, CAPT Forsberg and team are poised to develop three clinical decision support tools for use in men with advanced prostate cancer designed to estimate the likelihood of survival, disease progression, or skeletal-related events, at multiple time-points useful for medical and surgical decision-making. These models will be validated and formatted for use online (https://www.pathfx.org/) and will be integrated within the electronic health record in the Military Health System. These tools will help tailor decision-making and deliver more focused and cost-effective precision medicine to Military Health System beneficiaries. The protocol will leverage a large existing military cohort to apply Bayes' conditional probability theorem to develop prostate cancer-specific clinical decision support tools, using patient clinical and treatment characteristics to predict key study outcomes, including overall survival and metastasis, particularly to bone.

In February 2019, CAPT Forsberg and Dr. Cullen showcased their work, "Modeling Time from Bone Metastasis to Death in a Racially Diverse Cohort of Military Health Care Beneficiaries," at the American Society of Clinical Oncology, Genitourinary meeting. In this poster presentation, they discussed how patient race, treatment type, prostate specific antigen (PSA) value, and comorbid conditions predict overall survival of patients with prostate cancer after detection of bone metastasis. As shown in the graphic below, results indicated that the strongest predictors of survival were not race (1a), but instead treatment types (1b: radiation therapy, hormone therapy, chemotherapy, or a combination of the three) and the PSA level obtained closest to the time of diagnosis with bone metastasis (1c: proximal PSA).



The next steps for CAPT Forsberg and his team are to examine more patient-specific palliative care plans, while incorporating laboratory measures such as hemoglobin and white blood cell counts into their prediction tools to further assess survival in patients with prostate cancer. Lastly, the team plans to continue to study more racially/ethnically diverse patient populations using the International Bone Metastasis Registry.

Publications:

Forsberg JA, Wedin R, Boland PJ, and Healey JH. 2017. Can we estimate short- and intermediate-term survival in patients undergoing surgery for metastatic bone disease? *Clin Orthop Relat Res* 475(4):1252-1261. doi: 10.1007/s11999-016-5187-3.

Porcher R. 2017. CORR Insights(r): Can a multivariate model for survival estimation in skeletal metastases (PATHFx) be externally validated using Japanese patients? *Clin Orthop Relat Res* 475(9):2271-2273. doi: 10.1007/s11999-017-5434-2.

Combat Readiness-Medical Research Program

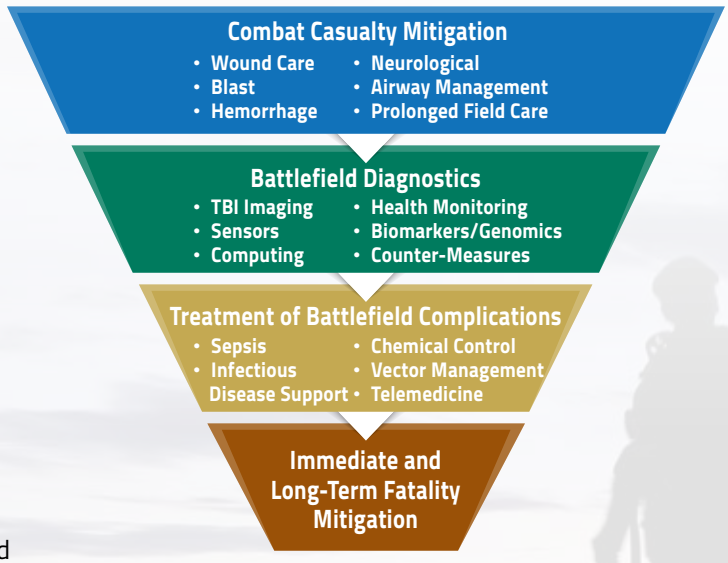
Vision: Deliver high-impact medical solutions throughout the continuum of care to increase survivability and readiness of the Warfighter in diverse operational settings

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

Program History

The Combat Readiness-Medical Research Program (CRRP) was established in FY19 with a congressional appropriation of $15M to pursue research related to forward-deployable solutions that can promptly address life-threatening injuries, medical threats, and treatments for Service members in battlefield settings. The FY19 Congressional language for the CRRP focuses on the immediate medical needs of the Warfighter on the battlefield following life-threatening injury or environmental exposure. Injuries or exposures include, but are not limited to, neurological injuries, hemorrhage, and exposures to chemical and biological threats. Synergistic topics related to medical combat readiness research have been supported by DHP Core and other Congressional Special Interest programs and managed by the CDMRP, such as the Defense Medical Research and Development Program, the Deployment Related Medical Research Program, the Joint Warfighter Medical Research Program, the Military Burn Research Program, the Peer Reviewed Medical Research Program, and the Psychological Health and Traumatic Brain Injury Research Program.

A request for information (RFI) was released and an inaugural Stakeholders meeting held to identify current research efforts and knowledge gaps in medical planning and resources for providing wounded Service members lifesaving care within the golden hour after an injury occurs, as well as medical capabilities that may mitigate fatalities. The RFI asked survey respondents to assess existing approaches and consider innovative technologies for extending trauma care through combat casualty mitigation, battlefield diagnostics, and treatment of battlefield complications (see figure on right). The results of the RFI, compiled from over 340 responses, were used to inform stakeholders of primed research, as well as cutting-edge and forward-looking solutions, to address delayed resuscitation, prolonged field care, and longer-distance en route care. The Stakeholders meeting brought together a diverse group of experts from non-profit organizations, academia, industry, and Government institutions. The information gathered through the Stakeholders meeting was published on the CRRP website (https://cdmrp.army.mil/crrp/default), and was used to inform the FY19 CRRP Programmatic Panel ahead of Vision Setting. During Vision Setting, the Programmatic Panel shaped the CRRP Vision, Mission, and investment strategy, and also distilled stakeholder-identified research priorities into CRRP Focus Areas for the Funding Opportunity Announcements in this initial program cycle.



Topics Areas Identified in FY19 CRRP Congressional Language for the Immediate and Long-Term Mitigation of Battlefield Fatalities.

FY19 Focus Areas

Scalable solutions for wound care that can address prevention of bleeding, infection, and acute pain; delivery of therapeutics (including non-opioid solutions for pain); and promotion of healing.

Decision-support solutions, such as algorithms, artificial intelligence, deep learning, and/or telemedicine, for triage and management of severely injured Warfighters, to include management and monitoring of:

- Acute pain
- Hemorrhage and resuscitation (e.g., airway management, control of bleeding, sedation, etc.)
- Multi-casualty events when delayed evacuation exceeds available capability and/or capacity, in order to extend provider capabilities.

Solutions addressing hemorrhage control, including:

- Non-compressible torso hemorrhage
- Alternatives to optimize logistics and administration of blood products to the Warfighter.

Wearable sensors with broader multiple capabilities to identify and monitor medical management of injuries, to include:

- Environmental exposures
- Onset of infection, including sepsis
- Physiological status (heart rate, blood pressure, respiration), stress monitoring tools
- Neurological injury
- Point-of-care imaging

FY19 Award Mechanisms

Rapid Development and Translational Research Award

The intent of the FY19 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 that 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 that can translate to advancements in civilian trauma care. This mechanism will support all CRRP Focus Areas.

"The CRRP Vision Setting consisted of experts in several fields. Although the CRRP is a new program, the Vision Setting gave great hope that we, as a community, can band together to ascertain the capability gaps and needs not covered by other medical research programs. These discoveries and solutions of our current limitations will be pivotal in order to provide the Warfighter the best care possible from the point of injury, through the recovery process, and into a quality of life that is due the Soldiers of our great country."

James West, SSG (US Army, Retired), CRMRP Programmatic Panel Member
Program Executive Office Aviation – Fixed Wing

"Given the fundamental changes anticipated in future battlefield scenario, the CRRP Stakeholders meeting was essential to focus researchers on gaps in medical readiness for forward trauma battlefield treatment. By bringing together stakeholders from widely different backgrounds, the meeting identified and addressed issues essential to the medical care of our forces. Bringing sustained medical care to the battlefield will require the integration of medical knowledge, science, and industry, particularly to address prolonged field care for such wide-ranging areas as burns, infectious disease, and massive hemorrhage. The meeting fundamentally changed my perspective on medical readiness."

Tina Palmieri, MD, CRMRP Stakeholder Meeting Participant
University of California Davis

Duchenne Muscular Dystrophy Research Program

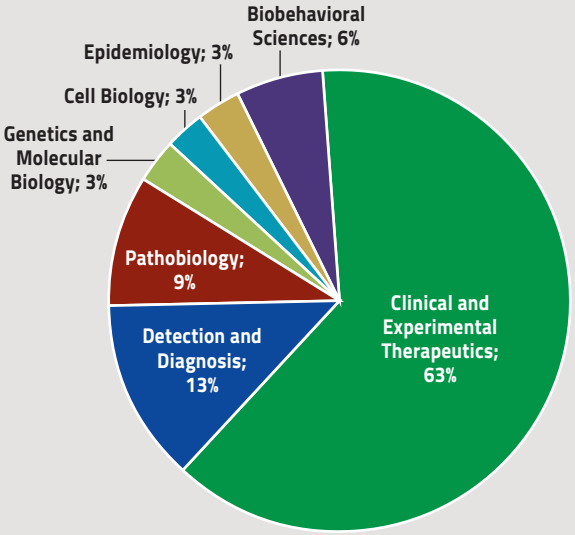
Vision: To preserve and improve the function and quality of life, and to extend the life span of all individuals with Duchenne

Mission: To better 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

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 Duchenne Muscular Dystrophy Research Program (DMDRP) was established in FY11 and has received $29.6M in congressional appropriations through FY19. The DMDRP has built a research portfolio of over 25 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.



FY11-FY18 DMDRP Portfolio Investment by SCS Code

"DMD has given me one thing that I value more than anything it has taken away from me. DMD gave me a sense of purpose..... I am thankful for being given the opportunity to serve as a Consumer Reviewer for the DMDRP. This role has allowed me to share my experience as a person living with DMD in a way that will help to shape the landscape of DMD research in the coming years."

Benjamin Dupree, DMDRP Consumer Reviewer

Improvements to Glucocorticoid Treatment

Eric Hoffman, PhD, John McCall, PhD, Kanneboyina Nagaraju, DVM, PhD, Formerly at Children's National Medical Center

- Screening identified compound VBP15 (renamed vamorolone) dissociated the harmful side effects of glucocorticoid steroids from their beneficial anti-inflammatory effects.
- Vamorolone demonstrated efficacy equal to prednisone in the treatment of muscular dystrophy, both in vitro and in vivo in the mdx mouse model of DMD.

Vamorolone is now in Phase 2b clinical trial testing as a potential replacement for glucocorticoid therapy (NCT03439670)

A Translational Pathway Toward a Clinical Trial Using the Second Generation AAV Micro-Dystrophin Vector

Dongsheng Duan, PhD, University of Missouri

- Showed that a one-time systemic treatment in young adult dystrophic dogs using AAV9 micro-dys resulted in persistent micro-dystrophin expression for 2 years.

Advanced Gene Therapy for Treatment of Cardiomyopathy and Respiratory Insufficiency in DMD

Barry Byrne, MD, PhD, University of Florida

- Developed clinically scalable platform of vector production.
- Showed that AAV9-miniDys improved cardiorespiratory function in dystrophic dogs.

Results from Drs. Duan's and Bryne's awards led to a collaboration with Solid Biosciences for a clinical trial evaluating µ-dys gene transfer (SGT-001) in adolescents and children with DMD (NCT03368742)

Optimization of Renin-Angiotensin-Aldosterone (RAA) Inhibitors as a Treatment for DMD

Jill Rafael-Fortney, PhD, Ohio State University

- Mineralocorticoid receptor (MR) antagonists work via preventing muscle membrane damage, inflammation, and fibrosis leading to the efficacy observed in DMD models and in cardiac outcomes in DMD patients
- MR antagonists work through the MRs present in skeletal muscle fibers to change gene expression, providing novel therapeutic targets for future drug development

Results from Dr. Fortney's award supported the rational for the trial Spironolactone Versus Prednisolone in DMD (NCT03777319)

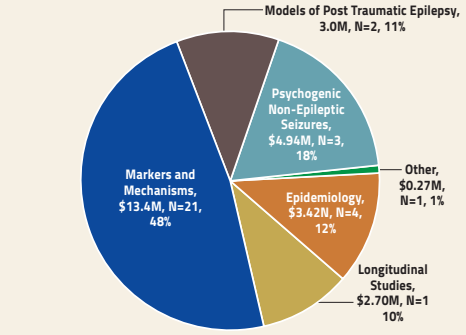
Epilepsy Research Program

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

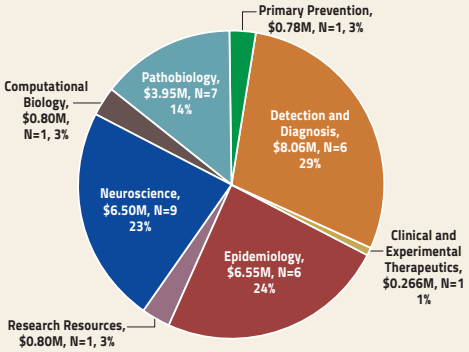
Mission: To understand post-traumatic epilepsy and associated comorbidities to improve quality of life, especially in Service members, Veterans, and caregivers

Program History

The DOD 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;[1] however, the mechanisms underlying this relationship remain unknown. The ERP has funded 32 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 (PNES), functional brain changes associated with PTE, and epidemiological studies of Service members. In FY19, the ERP offered two award mechanisms with the intent to solicit, innovative and impactful research in PTE.



FY15-FY18 ERP Portfolio Investment by Focus Area



FY15-FY18 ERP Portfolio Investment by SCS Code

Focus Areas

In FY19, the ERP offered the Idea Development Award and Research Partnership Award with the intent of soliciting novel, innovative research into the magnitude and mechanisms of PTE and to foster research partnerships that will address a problem or question in a manner that would be unachievable through separate efforts. The program has the following Focus Areas:

Markers and Mechanisms: Identifying markers or mechanisms of PTE in terms of biomarkers, therapeutic targets, early detection, diagnosis, prognosis, comorbidities, mortality, and risk stratification.

Epidemiology: Risk factor demographics, genetics, anatomy, pathology, or type of injury; differentiation between PTE and PNES; PTE outcomes; pre-existing conditions; and treatment and healthcare outcomes that characterize PTE following TBI.

Longitudinal Studies: Long-term evaluation of PTE including seizure frequency and severity; demographics, genetics, anatomy, pathology, or type of injury; comorbidities; latency between type of injury and PTE; mortality; treatment and healthcare outcomes research; and quality of life of individuals with PTE and their caregivers

Innovative research (Idea Development Award only): Tools that better inform or improve upon performance of PTE research including hardware/software platforms that improve seizure detection, characterization, or diagnosis; bio informatics strategies; development of new models or improvement of existing PTE models; and improve characterization of the circuits involved in PTE.

[1] Lowenstein DH. 2009. "Epilepsy After Head Injury: An Overview." *Epilepsia*. 50(Suppl. 2):4-9.

Deconstruction and Control of Neural Circuits in Post-Traumatic Epilepsy

Jeanne Paz, PhD, J. David Gladstone Institutes

The human brain comprises highly specialized regions that are interconnected and form circuits. These circuits coordinate our daily activities such as talking, recalling a fond memory, or even typing a message. After a TBI, reorganization of these circuits can lead to epilepsy, a phenomenon known as PTE. Understanding how circuits work in the healthy brain and how they are altered in response to injury could lead to effective treatments or preventative measures for PTE. Dr. Jeanne Paz, researcher at the Gladstone Institutes, is investigating a particular circuit that connects the outer portion of the brain (the cortex) with an inner region known as the thalamus.

This cortico-thalamo-cortical circuit enables sensation, perception, consciousness, and sleep. Dr. Paz's previous work revealed an important role for the thalamus in seizures. However, TBI usually results in damage to the cortex, and it is not known how that damage to the exterior of the brain might lead to internal damage and the development of seizures. Therefore, Dr. Paz is investigating how damage to the cortex affects the circuit this brain region forms with the thalamus.

Using advanced methods, Dr. Paz has generated new insights into how PTE develops in an animal model of TBI. Despite its location deep in the brain, the thalamus showed signs of significant damage after TBI, including inflammation and neuron death. Dr. Paz also showed that a key protein, C1q, was turned on, which prolonged the inflammatory response. Early data suggest that blocking C1q reduces inflammation and neuron loss. To advance C1q as a potential therapeutic target, Dr. Paz is investigating whether blocking C1q can prevent the development of PTE.

Post-Traumatic Psychogenic Seizure and Epilepsy Project

Hamada Altalib, DO, VA Connecticut Research and Education Foundation

PTE shares clinical hallmarks with similar, or perhaps co-morbid, conditions. PNES can clinically present as PTE; however, individuals with PNES have no EEG activity associated with their seizure events. Individuals with PNES are often misdiagnosed and will initially receive anti-epileptic medication that does not help them. It can be a long process for individuals with PNES to receive proper care. PNES is thought to be a condition that results from psychological stressors. Both PTE and PNES may co-exist in Service member populations. Understanding what makes PNES distinct from PTE in the clinic will make PNES detection easier and more accurate. This leads to better care for these individuals. By better understanding PNES, we improve care for individuals with both PTE and PNES. We also need to learn about what makes PTE so distinct from PTE after a head injury, through further study.

Little is known about the overlap or distinctions between PTE and PNES in Service members. The ERP is supporting a number of different studies ranging from advanced imaging to epidemiological and longitudinal studies. Dr. Hamada Atlalib, of the Veterans Affairs Connecticut Research and Education Foundation, is studying the frequency, risk factors, and health care outcomes of post-9/11 Veterans with PNES within the VA healthcare system. As part of the study, Dr. Altalib is looking at how TBI and PNES interact. Dr. Altalib has thus far shown that many of the individuals received treatment for PTSD prior to a PNES diagnosis. This preliminary finding was independent of gender. In male Service members, there was a high level of co-morbid TBIs. This highlights the complexity of outcomes from TBIs in male Service members. It suggests that TBIs can lead to either PTE or PNES, or both conditions. Combinations of both are also highly likely, highlighting the need for treatment and care that may need to address both in the same patient. Dr. Altalib is now investigating how anti-seizure drugs were used across the cohort to gain further insights.

"Post-traumatic epilepsy is a challenge to treat and manage its associated comorbidities. My hope is that the ERP will lead to the prevention of post-traumatic epilepsy and also improve treatment and quality of life for people with post-traumatic epilepsy and their caregivers."

Paul Rutecki, MD, University of Wisconsin-Madison

Gulf War Illness Research Program

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

Mission: Fund innovative Gulf War Illness research to identify effective treatments and accelerate their clinical application, improve definition and diagnosis, and better understand pathobiology and symptoms

Program History

The 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 MOMRP or intermittently through CDMRP. Since FY06, the GWIRP has received a total of $192M in congressional appropriations, including $22M in FY19. 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 greatest emphasis has been placed on identifying and testing potential treatments and objective measures and markers for 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.

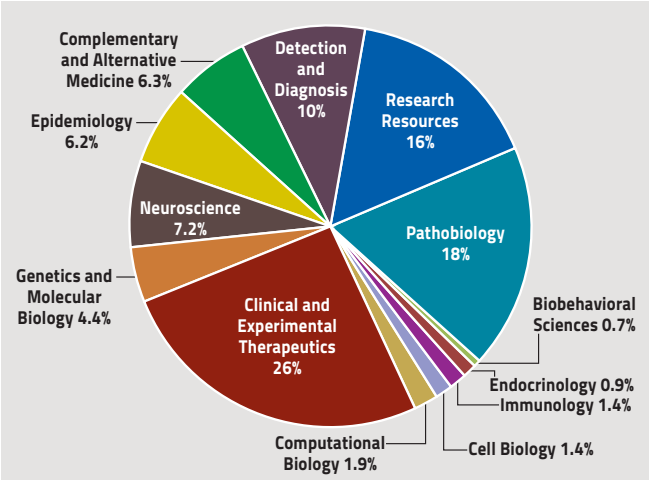
Overarching Challenges

The FY19 GWIRP requires all applications to address at least one of these overarching challenges:

- Revolutionize treatment and minimize side effects
- Eliminate the health consequences of GWI
- Distinguish symptom clusters to target treatments
- Identify what drives GWI and how to intervene
- Identify why GWI is worse for some than for others
- Validate determinants of GWI susceptibility, latency, and impacts on organs and systems

"With the understanding that quality research and development is a slow painstaking process and that 25+ years is a long time for Veterans to wait for answers, I am excited that Gulf War Illness research is moving towards more human subjects studies with practical applications. I have a deep respect for the entire CDMRP team and the fact that Consumer Reviewers are treated as equal partners. Overall, my experience has given me a renewed respect for the scientific process."

Vera Roddy, GWIRP Consumer Reviewer and Member of the External Advisory Board for the GWIRP-Supported Clinical Consortium



FY06, FY08-FY18 GWIRP Portfolio Investment by SCS Code

- Better define and diagnose GWI
- Determine whether GWI puts Veterans at greater risk for neurological diseases, cancers, or other conditions
- Help Veterans, their caregivers, and clinicians communicate effectively about GWI
- Develop primary prevention strategies based on theories of GWI etiology

GWI Treatment: Clinical trials with the potential to have significant impacts on the health and lives of Veterans with GWI continue to be a priority for the GWIRP. Examples of treatments currently in GWIRP-sponsored clinical trials are shown below.

Prednisone

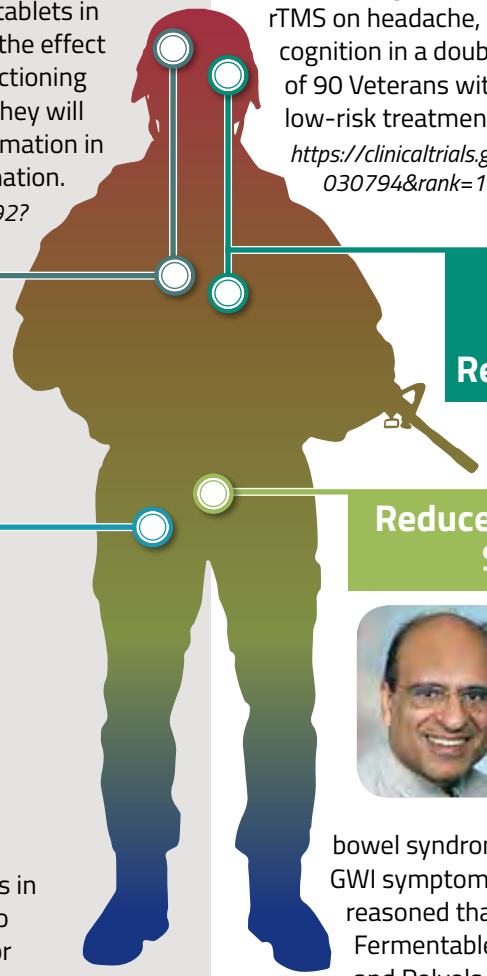
Ronald Bach, PhD

Center for Veterans Research and Education Foundation

Dr. Ronald Bach observed elevated inflammation in Veterans with GWI and hypothesized that prednisone, a potent anti-inflammatory agent, may serve as a treatment for this population. With FY13 GWIRP funding, Dr. Bach is conducting a double-blinded, placebo-controlled trial of low-dose delayed-release prednisone tablets in Veterans with GWI. His group will assess the effect of prednisone on physical and mental functioning pain, fatigue, and cognitive dysfunction. They will also monitor molecular markers of inflammation in blood as an objective measure of inflammation.

https://clinicaltrials.gov/ct2/show/NCT02506192?id=NCT02506192&rank=1

Improve Physical and Mental Well-being



Repetitive Transcranial Magnetic Stimulation (rTMS)

Albert Leung, MD

Veterans Medical Research Foundation of San Diego

Recent studies have shown that noninvasive rTMS of the motor cortex can reduce joint and muscle pain. This prompted Dr. Albert Leung to undertake clinical trials of rTMS in Veterans with GWI. With FY15 GWIRP funding, Dr. Leung is assessing the effects of rTMS on headache, muscle and joint pain, mood, and cognition in a double-blinded sham-controlled trial of 90 Veterans with GWI with the goal of validating a low-risk treatment for Veterans with GWI.

https://clinicaltrials.gov/ct2/show/NCT03030794?id=NCT03030794&rank=1

Improve Mood, Relieve Headache

Reduce Chronic Body Pain

Eliminate Post-Exertional Malaise

Curcumin versus Glutathione

Nancy Klimas, MD

Nova Southeastern University

Evidence of differential gene expression and blood-borne markers in Veterans with GWI led Dr. Nancy Klimas to conclude that the regulatory protein factor NF-κβ may play an important role in the regulatory imbalance associated with GWI. In a FY14 GWIRP-funded clinical trial, Dr. Klimas and her group are conducting a blinded, placebo controlled three-arm trial in 75 Veterans with GWI to assess and compare the abilities of the NF-κβ pathway inhibitors glutathione and curcumin to alleviate GWI symptoms and affect associated genes and molecular markers in the blood.

https://clinicaltrials.gov/ct2/show/NCT02848417?id=NCT02848417&rank=1

Reduce Gastrointestinal Symptoms

Low FODMAP Diet

Ashok Tuteja, MD

Western Institute for Biomedical Research

Many Veterans with GWI also suffer from irritable bowel syndrome and report worsening of GWI symptoms after eating. Dr. Ashok Tuteja reasoned that an intestine-friendly diet low in Fermentable Oligo-, Di- and Mono-saccharides and Polyols (FODMAPs) might reduce not only symptoms of irritable bowel syndrome, but also those of GWI. In a GWIRP-funded clinical trial, Dr. Tuteja is comparing the effects of low- and high-FODMAP diets in 68 Veterans with GWI. The trial will assess a low-FODMAP diet for effects on Veterans with GWI and GI symptoms.

https://clinicaltrials.gov/ct2/show/NCT02881944?id=NCT02881944&rank=1

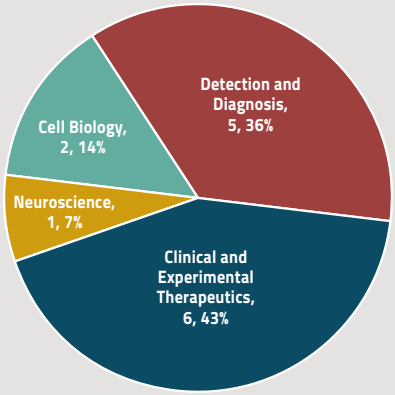
Hearing Restoration Research Program

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 Hearing Restoration Research Program (HRRP) was initiated in 2017 to pursue promising, necessary research for treatment of burdensome and very prevalent auditory system injury. It is estimated that more than 30 million Americans over the age of 12 years have hearing loss in both ears, and an estimated 48 million have hearing loss in at least one ear. In the military, the two most prevalent Service-connected disabilities are related to hearing disorders. The most recent data from the VA's Veterans Benefits Administration indicates that there are 1.1 million Veterans with Service-connected disability due to hearing loss. The HRRP will fund innovative research that has the potential to maximize operational effectiveness, medical readiness, and quality of life for Service members, Veterans and others living with significant auditory system injuries.



FY17-FY18 HRRP Portfolio Investment by SCS Code

FY19 Award Mechanisms

Focused Research Award

The FY19 HRRP Focused Research Award mechanism is intended to support promising research that will accelerate drug discovery and therapeutic development for hearing restoration or accelerate advances in the assessment, diagnosis, and treatment of auditory dysfunction.

Funding Level 1 supports exploratory, high-risk/high-reward research that is in the earliest stages of idea development

Funding Level 2 (with pilot clinical trial component option) supports the advancement of more mature research toward clinical translation

Focus Areas

- Develop or validate techniques/methods to assess, diagnose, or treat auditory dysfunction as related to synaptopathy, hidden hearing loss, and central auditory processing disorders
- Accelerate translation of biological regeneration/repair mechanisms into therapies that restore auditory function
- Develop reliable in-vitro human models for evaluating hearing restoration therapies

Therapeutic Function of Glucagonlike Peptide-1 for Hearing Restoration After Blast Exposure or Traumatic Brain Injury

Rong Gan, PhD, University of Oklahoma – Norman

Current clinical research on military personnel indicates strong correlation between TBI and sensorineural hearing loss. Blast-induced hearing damage shares common features with TBI-induced memory deficits, such as the loss of neurons in auditory cortex and spiral ganglion. The long-acting glucagon-like peptide-1 receptor agonist liraglutide, an FDA-approved drug for the treatment of type 2 diabetes, protects against and repairs neural damage from TBI or stroke in animal studies. Preliminary studies by Dr. Rong Gan's team indicate that liraglutide mitigates hearing damage after blast exposure in a chinchilla model. With support from a FY18 HRRP Translational Research Award, Dr. Rong Gan will further investigate the therapeutic effect of liraglutide on peripheral and central auditory pathways, as well as the mechanism by which liraglutide mediates neuroprotection and neuro-regeneration. Specifically, chinchillas will be exposed to a range of blast overpressure levels, both below and above the mild TBI threshold. The effect of liraglutide on neurotransmitter response, synaptic plasticity, oxidative stress, and cell apoptosis will be evaluated in relation with blast overpressure level and TBI severity. If successful, Dr. Gan's work will enable rapid translation of liraglutide into clinical trials to treat blast-induced hearing damage.

Novel Small-Molecule TrkB and TrkC Agonists for Cochlear Synaptic Regeneration

David Jung, MD, PhD, Massachusetts Eye and Ear Infirmary

According to the Veterans Benefits Administration, 1.1 million Veterans have a Service-connected hearing loss disability. Furthermore, irrespective of military Service, age-related hearing loss affects nearly two-thirds of adults 70 and older. Emerging evidence suggests that the synaptic connections between cochlear hair cells and spiral ganglion neurons (SGNs) are the most sensitive element to noise damage and aging. However, currently there is no treatment for cochlear synaptopathy. With support from a FY18 HRRP Translational Research Award, Dr. David Jung will explore a novel therapy to regenerate synapses between hair cells and SGNs. Building upon current understanding of the biology of SGN excitotoxicity, Dr. Jung's team will take a small-molecule approach to promote synaptogenesis along previously described signaling pathways involving tropomyosin receptor kinases (Trks) and neurotrophins. Specifically, small-molecule agonists of TrkB and TrkC will be target-delivered to cochlear bone using a novel conjugate. Their ability to stimulate neurite growth, regenerate synapses, and improve physiologic measures of hearing will be tested in mice as well as in non-human primates. If successful, Dr. Jung's work could potentially result in the first restorative therapy for cochlear synaptopathy.

"The HRRP provides a unique opportunity to fund cutting-edge research that is vitally important to military and civilian populations. Noise-Induced hearing loss continues to be one of the top Service-connected injuries for our Warfighters. The ability to hear and communicate is critical to the safety of each Warfighter, and is central to ensuring mission accomplishment worldwide. The collaborative work accomplished by key panel members from academia, federal government, military, and the VA ensures this funding is used on the best science with the highest potential to make major impacts. Outcomes from the HRRP will be far reaching and will benefit not only military members but all individuals worldwide suffering from the detrimental effects of permanent sensorineural hearing loss."

LTC Brandon Tourtillott, Clinical and Rehabilitative Medicine Research Program, HRRP Programmatic Panel Member

"The importance of addressing hearing loss is critical to helping improve both short and long-term outcomes for our warriors and their families. As a Veteran who suffers hearing loss from combat, I can attest that the work being done at CDMRP is crucial in solving multiple problems affecting our Service members. It is an honor to provide input on research that is focused on restoring hearing which may save a Soldier's life and will directly impact quality of life for the Service member and their family."

MSG (Ret) Bobby Ehring, HRRP Consumer Reviewer

Joint Warfighter Medical Research Program

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

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

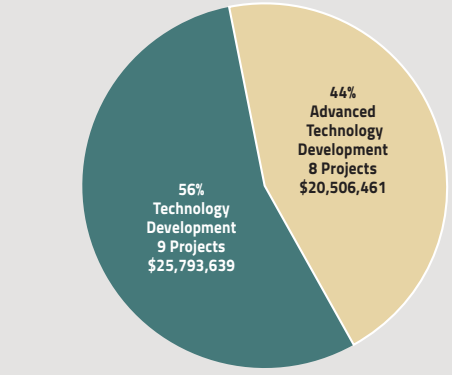
Program History

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

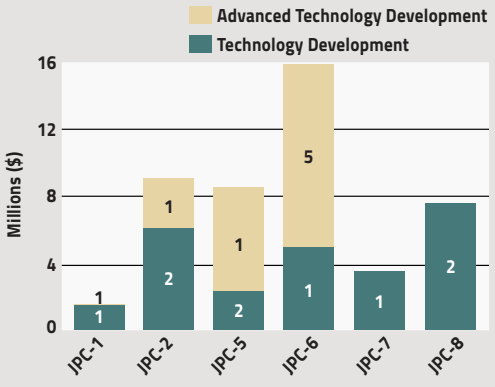
Each year, a broad spectrum of research projects are considered for funding under JWMRP. The projects align to the six JPCs scientific domains represented in DMRDP, including Medical Simulation and Information Sciences, Military Infectious Diseases, Military Operational Medicine, Combat Casualty Care,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

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

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.



FY18 JWMRP Investment
(% of total FY18 Investment)



FY18 JWMRP Final Funding Distribution
(Number of Awards Granted Indicated in Each Bar Chart)

Research and Product Development Efforts Funded by the JWMRP Include:

Focused effort on improving cognitive and functional deficits in individuals with traumatic brain injury using virtual technology

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

Phase IIb clinical trial for a Norovirus vaccine

Phase II malaria clinical trial with the first live attenuated vaccine against protozoal disease in humans

Phase I clinical trial for a direct acting polymyxin antibiotic to treat multidrug resistant gram-negative pathogens

Development and clinical trial of a food supplement to prevent travelers' diarrhea

Development of a lyophilized injectable for a point-of-care therapeutic for post-traumatic osteoarthritis

Development of an effective exposure psychotherapy paradigm for the treatment of PTSD

Device development of the Transportable Pathogen Reduction and Blood Safety System

Development of a non-electric, disposable intravenous infusion pump

Ultra-wideband wearable ultrasound probe for battlefield use

Development of a drug to prevent acute radiation syndrome and mitigate the delayed effects of acute radiation exposure

Accelerated product development of the opioid, Sufentanil, for pain treatment

Development of electronic capture and seamless communication of point-of-injury information using ultra-wideband technology integrated with the Nett Warrior Platform

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

Light-activated sealing to improve outcomes following penetrating bowel trauma

Pivotal study of non-invasive intracranial pressure assessment using a compact portable monitor on the regulatory pathway required for FDA de novo application process.

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 SCI

Development of a decision support tool with the ability to differentiate casualties who need a blood transfusion immediately upon arrival to a hospital from those who do not

Prosthetic with Moisture Management Liner and Active Cooling System

Ultrawide-Band, Wearable Ultrasound Probe for Battlefield Use

Non-Invasive Intracranial Pressure Assessment

Kidney Cancer Research Program

Vision: To eliminate kidney cancer through collaboration and discovery

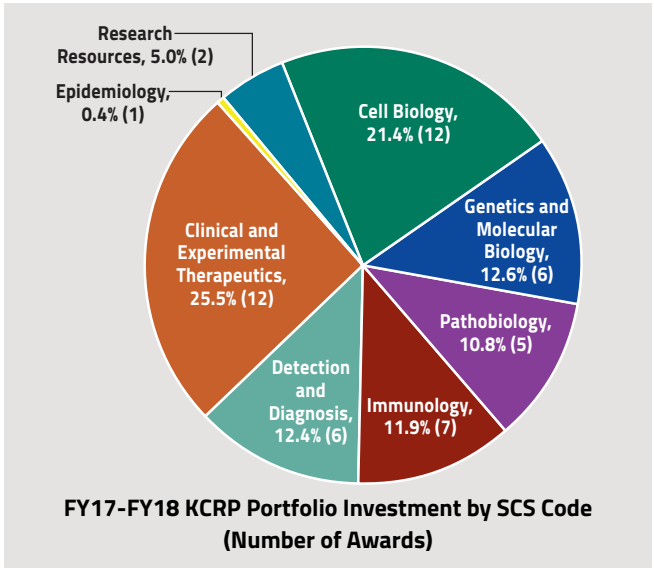
Mission: To promote rigorous, innovative, high impact research in kidney cancer for the benefit of Service members, Veterans, and the American public

Program History

The Kidney Cancer Research Program (KCRP) was established by Congress in FY17 with $10M to address critical research needs facing the Kidney Cancer community. As a result of the continued efforts of Kidney Cancer advocates, KCRP received congressional appropriations of $15M for FY18, and $20M directed to the program for FY19. The KCRP has funded 51 awards to support high-impact research in prevention, detection, treatment, and to bring talented investigators into the field. CDRMP funded kidney cancer and renal cell carcinoma research as a topic area under the PRMRP from FY06-FY09 and the Peer Reviewed Cancer Research Program FY10-FY16, for a total combined investment of $13.2M. For FY18, KCRP offered funding mechanisms designed to foster innovative research, provide opportunities for early-career investigators, mentor and prepare physicians for productive Kidney Cancer research careers, advance emerging technologies to aid patient outcomes, and support collaborations between clinicians and scientists.

KCRP's Military Relevance

Cigarette smoking, historically more prevalent among Veterans, is the strongest known risk factor for the development of renal cell carcinoma.[1,2] Other occupational exposures unique to active Service, such as ionizing radiation or chemical and/or hazardous materials can cause kidney cancer, although the disease may not appear until later in life. This results in Veterans being more frequently affected than their US civilian counterparts.



FY17-FY18 KCRP Portfolio Investment by SCS Code (Number of Awards)

"Our government and citizens should be proud of the efforts undertaken [by] the KCRP. Our tax dollars are being put to work to attack a health care problem that has been sorely underfunded for some time. The cutting edge research, the impact on the warfighter and their family and loved ones, and the hope this research inspires provides an incalculable return on our taxpayer investment."

Bryan Lewis, KCRP Consortium Development Award External Consumer Advisor

[1] McLaughlin JK, Hrubec Z, Heineman EF, et al. (1990). Renal cancer and cigarette smoking in a 26-year followup of US Veterans. *Public Health Rep.* 105: 535-537.

[2] Talcott GW, Cigrang J, Sherrill-Mittleman D, et al. (2013) Tobacco use during military deployment. *Nicotine Tob Res.* doi:10.1093/ntr/nts267

KCRP Investment in Rare Kidney Cancers:

In FY18, KCRP Programmatic Panel members recommended funding four awards investigating rare and under-studied subtypes of kidney cancer. These studies represent 15% of the total number of awards recommended for funding during this fiscal year.

Defining the Role of Beta-Catenin Activation on Wilms Tumor

Signals from developing renal stroma guide nephron progenitor cell maturation, and disruption of these signals is associated with nephrogenic rests seen in the pediatric kidney cancer, Wilms tumor. With support from an FY18 Physician Research Award, Dr. Keri Drake will determine if stromal activation of beta-catenin regulates stroma-to-nephron progenitor interaction and how this signaling may promote Wilms tumorigenesis.

Biological Determinants of Kidney Cancer Health Disparities

African Americans have a higher incidence of clear cell renal cell carcinoma than European Americans. Recipient of an FY18 Concept Award, Dr. Khadijah A. Mitchell will make genome-wide comparisons of African American and European American populations to identify the biological determinants of clear cell renal cell carcinoma among African Americans.

FY17–FY18 KCRP Idea Development Award – Early Career Investigator

KCRP recognizes the need to provide funding to young investigators for innovative Kidney Cancer research

Immunotherapy	Metabolism
John Wilson, PhD, Vanderbilt University *Reinvigorating Antitumor Immunity in Renal Cell Carcinoma with Nanoparticulate STING Agonists*	**Ching-Hsien Chen, PhD,** University of California, Davis *Targeting IGF1R Signaling in MTAP-Deficient Kidney Cancer*
Drug Development	**Regulation of the Immune Response**
Arun Iyer, PhD, Wayne State University *Tumor Stroma-Penetrating Oligomicelles Containing Combination Payload for Reversal of Drug Resistance and Immune Modulation in Kidney Cancer*	**Kathleen Mahoney, MD, PhD,** Dana-Farber Cancer Institute *Is VISTA:VSIG3 an Actionable Immune Checkpoint Target in Kidney Cancer?*
Chromosome Structure	**Oncogenes**
Srinivas Viswanathan, MD, PhD, Dana-Farber Cancer Institute *Genomic and Functional Analysis of Translocation Renal Cell Carcinoma*	**Laura Banaszynski, PhD,** University of Texas, Southwestern Medical Center at Dallas *Chromatin Dysregulation and Metabolism Disorder in Kidney Cancer*

"We are seeing a surge of interest in kidney cancer, particularly among young investigators who bring exciting and novel ideas into the investigations that will both transform the science of kidney cancer and translate into new therapies, and create a committed workforce that is focused on this set of cancers that arise in the kidney"

W. Kimryn Rathmell, FY19 KCRP Programmatic Panel Chair

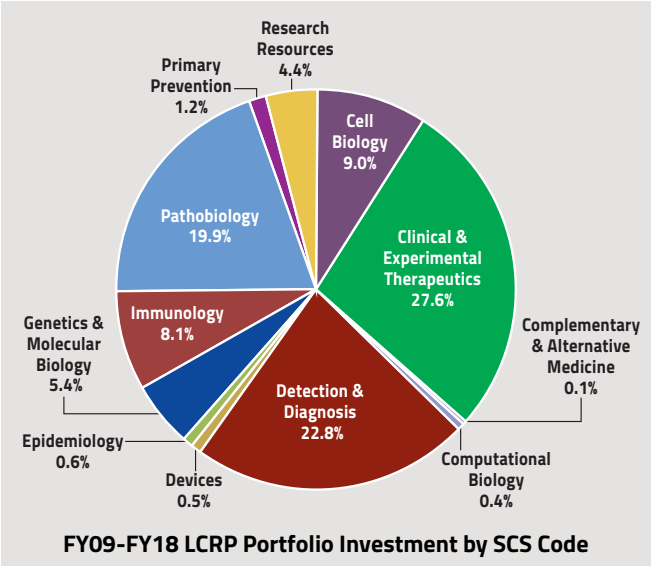
Lung Cancer Research Program

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

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

Program History

The DOD 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 $141.5M in congressional appropriations through FY19. Over the past 10 years, the LCRP has played a critical role in helping to accelerate high-impact translational research, encouraging innovation and stimulating creativity, bringing new investigators into the lung cancer field, and facilitating the creation of unique partnerships and resources.



FY09-FY18 LCRP Portfolio Investment by SCS Code

Strategic Priorities/ Areas of Emphasis

Anyone can get lung cancer, whether you are a smoker, former smoker, or never smoker. Despite improved screening methods for lung cancer and advances in treatment, the 5-year survival rate remains extremely poor at 18%. The LCRP recognizes there are a broad range of unanswered research questions that are potentially critical to advancing prevention, detection, treatments, and cures for lung cancer. To meet this substantial need, the FY19 LCRP requires all applications to address at least one of the following areas of emphasis:

- Identify innovative strategies for the screening and early detection of lung cancer
- Understand the molecular mechanisms of initiation and progression to clinically significant lung cancer
- Identify innovative strategies for prevention of the occurrence of lung cancer
- Identify innovative strategies for the treatment of lung cancer
- Identify innovative strategies for the prevention of recurrence of or metastases from lung cancer
- Develop or optimize predictive markers to assist with therapeutic decision-making
- Understand mechanisms of resistance to treatment (primary and secondary)
- Understand contributors to lung cancer development other than tobacco
- Identify innovative strategies for lung cancer care delivery (clinical management/surveillance/symptom management)

Reviewer Perspective

"Serving as a scientific reviewer for the CDMRP Lung Cancer Research Panel is a highlight of my year. The panels are incredibly well balanced between scientists, translational researchers, and patient advocates. Each panel allows me to gain valuable insight into state-of-the-art techniques for lung cancer research, but also connects me to key thought leaders in the field. I have grown immensely as a scientist and clinician through these interactions. More importantly, work funded by the CDMRP has led to groundbreaking advances in lung cancer which has directly benefitted all types of patients with lung cancer, particularly military Veterans. I could not be more proud to serve as a scientific reviewer for such an important cause."

Brenden Stiles, MD, LCRP Peer Reviewer

Research Portfolio

Investigating the Role of the Lung Microbiome in Non-Small Cell Lung Cancer Tumor Initiation and Progression

Chengcheng Jin, PhD, Massachusetts Institute of Technology

With support from an FY14 LCRP Concept Award Dr. Chengcheng Jin investigated the role of the commensal microbiota of the lung in promoting non-small cell lung cancer (NSCLC) development. Sequencing analysis comparing the bacterial DNA in the lungs to that in stool samples revealed that distinct bacterial communities existed within the lung versus the gut. Dr. Jin also discovered that development of lung adenocarcinoma was associated with increased total bacterial burden in the lung and airway tissue, as well as an alteration of the microbiota composition as compared to cancer-free mice.

The results supported by the LCRP award enabled Dr. Jin to further investigate the role of commensal microbiota in regulating tumor initiation and progression in the lung by comparing germ-free mice to conventional mice with normal microbiome. In the germ-free, aseptically raised animals, both tumor burden and number were substantially decreased. Moreover, combined antibiotic treatment with ampicillin, neomycin, metronidazole, and vancomycin resulted in significantly reduced tumor burden in the conventional mice but failed to inhibit tumor cell growth in vitro, highlighting the critical role that intact commensal microbiota in the lung play in promoting tumorigenesis. Currently, Dr. Jin is investigating host immune pathways involved in mediating the effect of the lung microbiome on tumor development. Thus far, results confirm that tumor progression is associated with increased bacterial burden and immune activation in the lung. These findings provide strong evidence that manipulation of the microbiota in the lung could lead to new treatment strategies.

Jin C, Lagoudas GK, Zhao C, et al. 2019. Commensal microbiota promote lung cancer development via γδ T cells. *Cell.* 176(5):998-1013.

Clinical Trial Testing of an Immune Checkpoint Inhibitor Plus Stereotactic Ablative Radiotherapy in Patients with Inoperable Stage I Non-Small Cell Lung Cancer

Karen Kelly, MD, University of California, Davis

Patients with inoperable stage I NSCLC are treated with stereotactic ablative radiotherapy (SABR), a precisely focused radiation technique; however, 30% of patients develop recurrent disease that is fatal within 3 years. Unfortunately for these patients, conventional chemotherapies are typically not well tolerated and are contraindicated due to the same clinical features that preclude initial surgical resection. A systemic therapy showing promise uses a new class of drugs, immune checkpoint inhibitors (ICIs), which exploit the immune system to target and kill tumor cells. With support from a LCRP FY14 Clinical Exploration Award, Dr. Karen Kelly is testing systemic delivery of atezolizumab, an anti-PD-L1 antibody, combined with SABR in a first of its kind clinical trial focused in early stage lung cancer patients with inoperable disease. Radiation therapy, like SABR, is a well-known mediator of the immune response and will partner with the ICI to enhance the body's immune response against tumor cells and promote tumor cell death.

In this novel Phase I dose finding study, atezolizumab plus SABR was well tolerated, and no additional safety signals were reported. The standard dose of atezolizumab will be evaluated in subsequent trials. Interestingly, 3 of 12 patients had a partial response to two cycles of induction atezolizumab prior to SABR, and no patient progressed during induction therapy.

These exciting early results from this Phase I LCRP-funded study have spurred the National Cancer Institute's sponsorship (through their National Clinical Trials Network) of trial SWOG/NRG S1914 entitled, "A randomized Phase III trial of SBRT with or without atezolizumab in early stage inoperable NSCLC patients," scheduled to begin enrollment late in the fall of 2019.

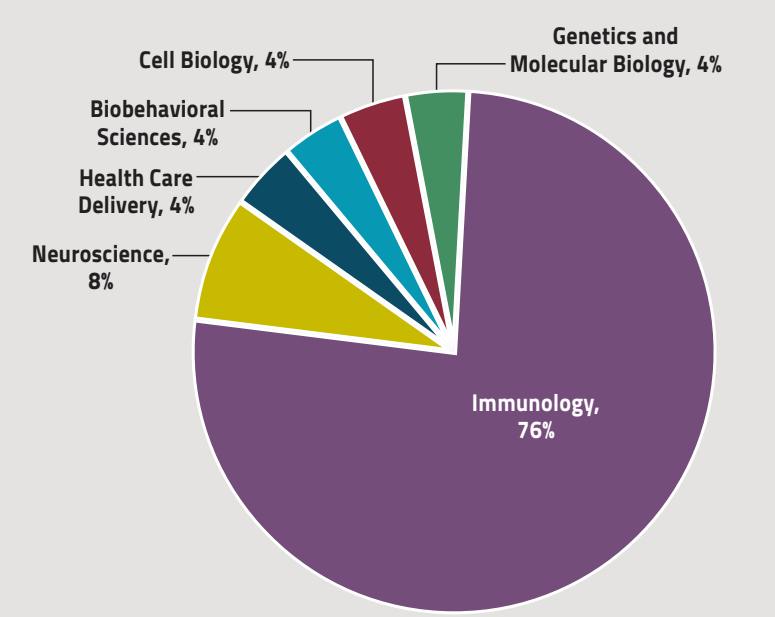
Lupus Research Program

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 causes 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.



FY17-FY18 LRP Portfolio Investment by SCS Code

Treatment options for lupus are highly dependent on an individual patient's symptoms and can include NSAIDs 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 Review Medical Research Program from FY05-FY16. During this time, the PRMRP funded 21 lupus research awards for a total of $20.6M. In FY17 the Lupus Research Program (LRP) was established with an appropriation of $5M. Since then, a total of $15M has been appropriated to the program, including $5M in FY19. The LRP has funded 25 awards through FY18 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.

Targeting IRF5 Hyperactivation in SLE as a Driver of Disease Risk and Pathogenesis

Betsy Barnes, PhD, Center for Autoimmune, Musculoskeletal, and Hematopoietic Diseases, The Feinstein Institute for Medical Research

Systemic lupus erythematosus (SLE) is an autoimmune disorder that causes inflammation in numerous tissues within the body and a wide range of symptoms including fatigue, arthritis, headaches, organ damage, seizures, and strokes. Because of the variety of symptoms a patient with SLE may experience, it is often difficult to diagnose and treat. This issue is exacerbated by the fact that the physiological mechanisms underlying SLE are still largely unknown. While the specific causes of SLE remain unclear, genetic risk factors and environmental stressors have been identified that are known to contribute to the disease's development and progression.

Previous research has suggested that there is a genetic association between certain genetic variants of interferon regulatory factor 5 (IRF5), a protein that controls inflammatory and immune responses, and SLE. Specific variants are associated with elevated IRF5 expression and pro-inflammatory cytokine production. The variants are strongly associated with an increased risk of developing SLE and contribute to what is referred to as the *IRF5*-SLE risk haplotype. In 2010 and 2012, Dr. Betsy Barnes and her colleagues investigated the relationship between the risk haplotype and IRF5 expression and activation. The results of her two studies showed that IRF5 expression was enhanced by the risk haplotype, and that IRF5 was significantly activated in specific immune cells of patients with SLE.[1,2] Taken together, these results suggest that genotype is not the sole driver of IRF5 activation in SLE. Further research is required to understand how IRF5 activation contributes to SLE disease symptoms and severity.

In FY17, Dr. Barnes was awarded a LRP Impact Award to build upon her previous work and investigate whether IRF5 hyper-activation is a driver of SLE onset and severity and whether or not its inhibition will mediate protective effects in a spontaneous murine lupus model. To answer these questions, Dr. Barnes will investigate three major hypotheses: (1) whether the IRF5 risk haplotype is cell specific and drives hyper-activation of IRF5, (2) whether inhibition of IRF5 activation will mediate protection against the IRF5 risk haplotype and SLE disease severity, and (3) whether treatment of a spontaneous lupus murine model with an inhibitor of IRF5 activation will improve disease outcomes long-term. The results of this project have the potential to make a significant impact on the lives of individuals living with lupus. In addition to providing functional and mechanistic insight into SLE progression, the findings of this project will provide clarity into the molecular drivers of SLE disease onset and mortality. Of critical importance to lupus patients, this study may provide the first evidence to support targeting IRF5 hyper-activation as a novel treatment for SLE.

References

[1] Feng D, Stone RC, Eloranta ML, et al. 2010. Genetic variants and disease-associated factors contribute to enhanced interferon regulatory factor 5 expression in blood cells of patients with systemic lupus erythematosus. *Arthritis Rheum.* 62(2):562-573. doi: 10.1002/art.27223

[2] Stone RC, Feng D, Deng J, et al. 2012. Interferon regulatory factor 5 activation in monocytes of systemic lupus erythematosus patients is triggered by circulating autoantigens independent of type I interferons. *Arthritis Rheum.* 64(3):788-798. doi: 10.1002/art.33395

"Consumer reviewers provide a unique perspective in peer review that is both rewarding and essential to the process. I think of my role there as to provide the laymen report of how each study will affect the patient."

Molly McCabe, Lupus Research Alliance, LRP Consumer Peer Reviewer

Melanoma Research Program

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

"The dedicated MRP is a long-awaited goal for our field, and the broad participation in our Stakeholder's meeting signals the need and the opportunity to accelerate progress in melanoma, which has gone from being a cancer without survival-improving medical options, to one for which we consider the opportunity for cure for all of our patients, even with inoperable disease."

John Kirkwood, MD, Chair, MRP Panel

Program History

According to the National Cancer Institute, there were 91,270 new cases of melanoma diagnosed in the US during 2018. Melanoma cases have been increasing steadily over the last 40 years. It is the fifth most common type of cancer in the United States, representing 5.3% of all new cancer diagnoses every year. Melanoma is of particular interest to the US military because active duty Service members spend prolonged periods outside, especially during deployment. Recent studies suggests that exposure to high levels of solar radiation in young adulthood is associated with a higher risk of melanoma mortality. Melanoma diagnoses are increasing among active duty Service with the greatest incidence rates in the Air Force, Navy, and the Marines. Given the extreme and harsh conditions Service members face in theater and the rise of this aggressive and frequently deadly form of cancer, the US Congress established the Melanoma Research Program (MRP) in the DOD appropriation with an appropriation of $10M. With this new program, MRP will invest 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. In the inaugural year, the MRP sets forth a challenge (see next page) for the research and clinical community to change the approach to melanoma prevention, treatment, and long term care.

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.

Riemenshneider K, 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.

FY19 MRP Funding Opportunities

Award Mechanism	Key Elements	Funding
Concept Award	Supports the exploration of highly innovative, untested, potentially groundbreaking concepts in melanoma.	Maximum funding of **$75,000** for direct costs (plus indirect costs) for up to 1 year.
Idea Award	Supports new ideas that represent innovative, high-risk/high-gain approaches to melanoma research.	Maximum funding of **$300,000** for direct costs (plus indirect costs) for up to 3 years.
Team Science Award	Supports new or existing partnerships between two or three independent investigators focusing on synergistic research that will significantly advance the field.	Maximum funding of **$700,000** for direct costs (plus indirect costs) for up to 3 years.
Translational Research Award	Supports studies aiming to leverage existing biobanks, biorepositories, ongoing or completed clinical trials to address a translational question or problem in melanoma.	Maximum funding of **$600,000** for direct costs (plus indirect costs) for up to 3 years.

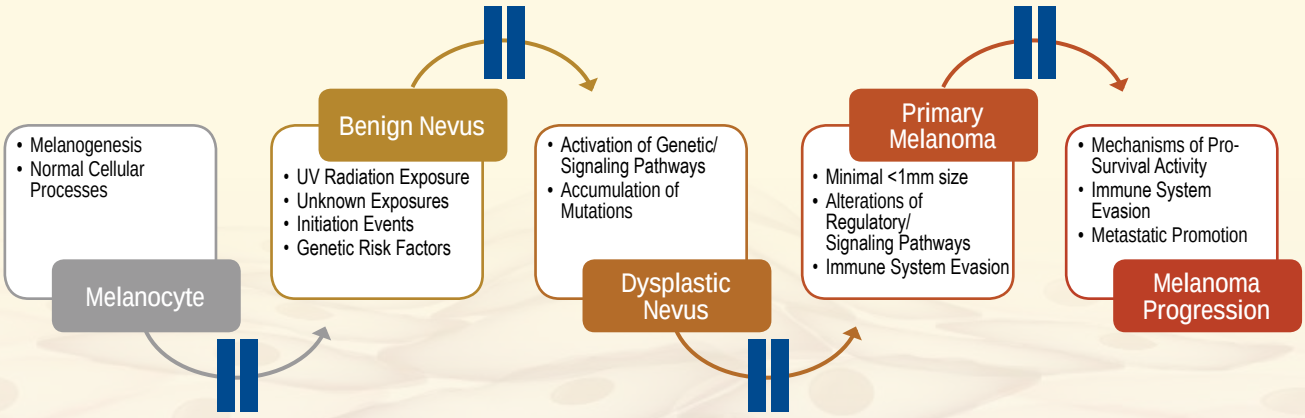
FY19 Melanoma Research Program Challenge Statement

The MRP challenges the research community to ***redefine*** the concept of prevention. Melanomagenesis is a multi-step process initiating from normal melanocytes to dysplasia through the development of melanoma and metastasis. A new paradigm of prevention may include stopping the initiation of dysplasia, halting the progress to malignancy, or blocking micro-metastases. The MRP acknowledges that each step along the disease process from initiation to metastasis is an opportunity to impede any further cancer progress and to effect a cure. The MRP challenges the research community to prevent melanoma earlier in the disease process thus preventing metastasis. The melanoma clinical, research, and patient community traditionally view prevention as the use of sunscreen/blockers to protect the melanocyte from harmful ultraviolet (UV) radiation. The MRP recognizes the usefulness of this strategy while tasking the research community to *redefine prevention to include the entire melanomagenesis process*. This is especially critical in rare subtypes of melanoma where traditional sunscreen blockers are not applicable. Rare melanoma subtypes (i.e., acral, uveal, and mucosal) may not be initiated by exposure to UV radiation like cutaneous melanoma. Taken together, the MRP looks to shift the paradigm of prevention of all types of melanoma by investing in research studies focused on eliminating the progress of this deadly disease whether it is cutaneous melanoma or a rare subtype.

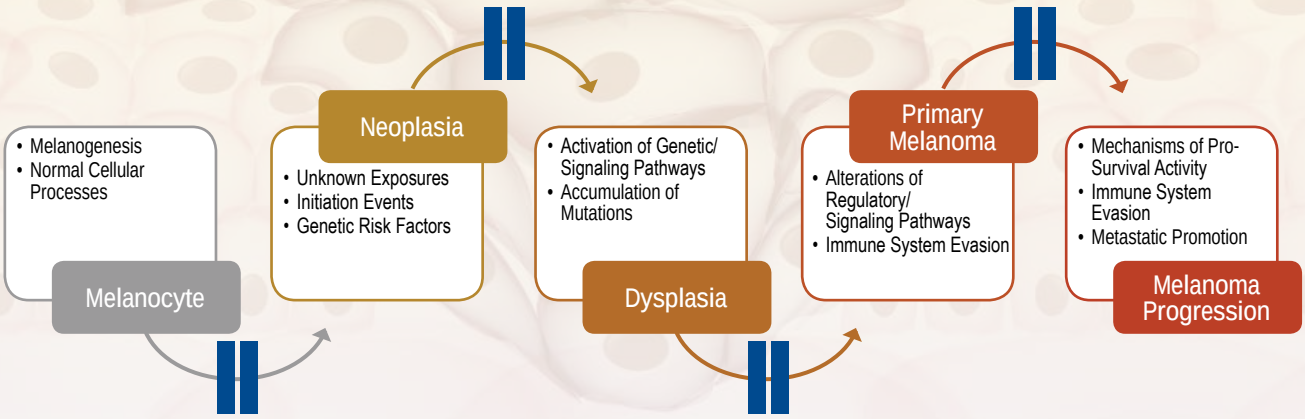
"AIM is proud to be a stakeholder for the MRP. It is high-impact research programs like this that are critical to finding new treatments for melanoma."

Valerie Guild
MRP Consumer Reviewer, Programmatic Panel

Prevention of Cutaneous Melanoma Evolution



Prevention of Melanoma (Rare Subtypes) Evolution



Military Burn Research Program

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

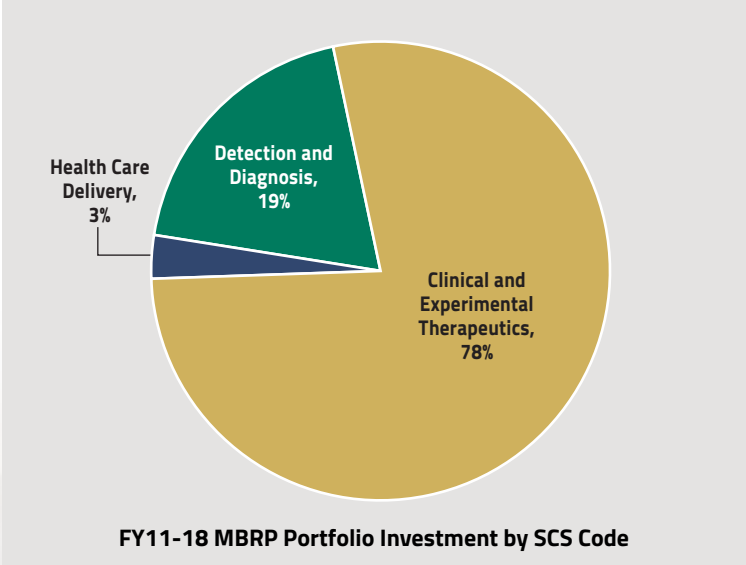
Mission: Identify and address gaps in burn trauma care through military focused translational research

"The consumer advocate provides the MBRP team with a unique patient perspective and lessons learned from the battlefield to help tailor burn-related research and products to the unique qualities of the battlefield environment."

Lt Col (Ret) Bryan Forney
MBRP Consumer Reviewer

Program History

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.[1] Burns have comprised some 5%-20% of the casualties sustained in post-World War II conflicts.[2] From 2006-2018, the Defense Medical Epidemiology Database reports nearly 130,000 ambulatory visits with a primary burn injury diagnosis code among active component Service members. The mean total healthcare cost per burn patient in high income countries has been estimated at $88,218 (range $704-$717,306).[3]



FY11-18 MBRP Portfolio Investment by SCS Code

The DOD Military Burn Research Program (MBRP) was initiated in 2011 to address capability gaps for treating combat burn injuries. These gaps, identified by subject matter experts on the MBRP Programmatic Panel, address burn injuries obtained from the point of injury to treatment at stateside Military Burn Centers.

Through FY18, MBRP has funded 37 projects intended to support preclinical and clinical research across nine topic areas that have resulted in the advancement of novel therapies to treat burn wounds while impacting the current standard of care for treating burn-injured Service members, Veterans, and the general public. These continued efforts, in concert with the program's successes, have resulted in more than $70M in congressional appropriations through FY19.

[1] Kauver DS, Cancia LC, Wolf SE, et al. 2006. Comparison of combat and non-combat burns from ongoing US military operations. *J Surg Res* 132:195-200.

[2] 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):453-460.

[3] Hop, MJ, Polinder, S., van der Viles CH, et al. 2014. Costs of burn care: A systematic review. *Wound Repair Regen* 22(4):436-450.

Rodney Chan, MD

Decreasing Skin Graft Contraction Through Topical Wound Bed Preparation with Anti-Inflammatory Agents, *USAISR*

Dr. Chan and his team determined that the outcome of anti-inflammatory modulation to decrease skin graft contraction was affected by the timing of its application. Whereas the application of anti-inflammatory agents to modulate the wound bed prior to application of a split-thickness skin graft inevitably led to graft failure, even when applied in small dosages, possibly due to the inhibition of angiogenesis and migration of essential nutrients to the graft, the application of these same agents after skin graft take resulted in decreased contraction and improved skin quality as compared to untreated controls. A clinical study is planned to further investigate these findings for patients prone to skin graft contraction.

Ingrid Parry, MS, PT, BT-C

A Goniometry Paradigm Shift to Measure Burn Scar Contracture in Burn Patients, *USAISR*

Ms. Parry and her team developed a more valid protocol for goniometry (measuring angular position of limbs rotating around a joint) to better measure the true restriction of motion caused by burn scarring. This revised goniometry protocol is more pertinent and informative when measuring range of motion outcome with the burn injured population.

Saman Arbabi, MD

Topical Modulation of the Burn Wound Inflammatory Response to Improve Short and Long Term Outcomes, *University of Washington*

Dr. Arbabi's team determined that topical inhibition of p38 MAPK in the red Duroc burn wound model modifies initial wound inflammatory responses and subsequent remodeling but does not impact final scarring outcomes. These results enhanced previous findings from the same group that demonstrated topical inhibition of p38 MAPK attenuated systemic inflammatory response and improved outcomes in a murine model."

Joseph Solomkin, MD, FACS, FIDSA

Antimicrobial Block Copolypeptides (A-Blocks): Innovative Therapeutics and Prophylactics for Wound Infection, *University of Cincinnati*

Dr. Solomkin and his team have shown efficacy in two products to treat both open and closed wound infections. The first product, Amicidin alpha, is a surgical gel that combines microbicidal activity and barrier properties within the same molecule. The molecule has been shown to be effective in the prevention and treatment against MRSA and *P. aeruginosa* infections in porcine open wound and rodent closed wound models. Secondly, Amicidin beta is a solution that combines microbicidal activity and surfactant properties within the same molecule for enhanced intrawound performance. This molecule has been shown to have concentration-dependent anti-biofilm properties in an ex vivo porcine skin explant model with P. aeruginosa.

Clinical Trials Funded by the MBRP in 2018

Principal Investigator	Project Title	Objective
Richard Clark, MD NeoMatrix Therapeutics, Inc.	A Phase 1 Randomized, Placebo-Controlled, Single Ascending Dose Study to Examine the Safety, Tolerability, and Pharmacokinetics of cP12 in Healthy Adults	Determine the safety of cP12 in healthy volunteers for the purpose of limiting burn injury progression.
Celeste Finnerty, PhD University of Texas Medical Branch, Galveston	Application of Adipose-Derived Stem Cells as an Antiscarring Therapy Following Massive Burn Injuries	Determine whether a burn patients own adipose derived stem cells can be used to improve wound healing and decrease burn scarring.
Jonathan Friedstat, MD Massachusetts General Hospital	A Within-Scar, Randomized Control Trial Comparing Fractional Ablative Carbon Dioxide Laser to Non-Energy-Based, Mechanical Tissue Extraction and No Treatment	Evaluates whether a fractional ablative CO_2 laser treatment can improve functional outcomes from hypertrophic burn scars.
Benjamin Levi, MD University of Michigan	Continuous, Portable, Non-Perfusion Based 'Short Wave Assessment Tool' (SWAT) Improves Burn Care	Validate a novel point-of-care, portable imaging device that provides objective information about burn depth to guide targeted treatments to improve patient outcomes.

Multiple Sclerosis Research Program

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

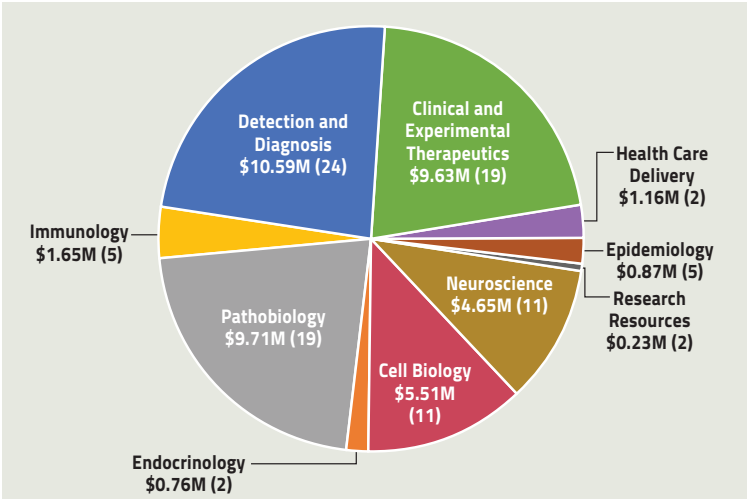
Mission: To support pioneering concepts and high impact research relevant to the prevention, etiology, pathogenesis, assessment, and treatment of multiple sclerosis for the benefit of Service members, Veterans, and the American public

Program History

Multiple sclerosis (MS) is a chronic, potentially disabling disease of the central nervous system which can manifest in many ways across the MS patient population. Common manifestations include pain, numbness, fatigue, vision problems, muscle spasms, mobility difficulties, bladder and bowel issues, sexual dysfunction, cognitive changes, and depression. Although MS affects nearly 1 million individuals in the United States, its cause is still not known. Scientist believed that MS is triggered by a combination of genetic and environmental factors. While individuals of all ages are affected by MS, it is more commonly diagnosed in young adults, particularly women, between the ages of 20 and 50. Currently, there is no cure for MS. Through the passionate efforts of MS advocates, the Multiple Sclerosis Research Program (MSRP) was established in FY09. The initial congressional appropriation was $5M, since then, a total of $57.1M has been appropriated to the program, including $6M in FY19.

"Serving as a CDMRP MSRP consumer reviewer was an intimidating prospect but it turned out to be an incredible experience. My reviews were always thoughtfully considered and treated with the same level of significance as those from the scientific and clinical expert reviewers. I became acquainted with several of the panel members personally and really felt that I was contributing to an important process."

Jim Turk, National Multiple Sclerosis Society, MSRP Consumer Peer Reviewer



FY09-FY18 MSRP Portfolio Investment by SCS Code

Through FY18, the MSRP funded 100 awards to support the exploration of innovative concepts or untested theories in high-risk/potentially high-reward research; development of readily accessible, cost-effective, validated analytical methods; multidisciplinary collaborations; development of translational collaborations among clinicians and research scientists from within and outside the MS field to move ideas into clinical applications; and pilot clinical trials to evaluate innovative interventions that could have a profound impact on the management of MS symptoms.



Mitochondrial Dysfunction and Disease Progression in MS

Patrizia Casaccia, MD, PhD, Icahn School of Medicine at Mount Sinai and Advanced Science Research Center at The Graduate Center of The City University of New York

Ilana Katz Sand, MD, Icahn School of Medicine at Mount Sinai

Catarina Quinzii, MD, Columbia University

MS is a demyelinating disease characterized by lesions and an underlying neurodegenerative process, which is more prominent in patients with progressive disease. While mitochondrial dysfunction has been proposed to underlie the neuronal damage, the precise mechanism remains unknown.

With support from a FY14 Investigator-Initiated Partnership Award, Drs. Casaccia, Katz Sand, and Quinzii along with their collaborators, Drs. Matilde Inglese and Valentina Fossati have been studying how extrinsic and cell intrinsic factors modulate neuronal bioenergetics potentially contributing to MS progression. The researchers conducted a morphological and functional screening of mitochondria in neurons exposed to the cerebrospinal fluid of MS patients with relapsing remitting or progressive disease. Their data suggest neuronal mitochondrial impairment and altered energetic metabolism as the underlying basis for neurodegeneration in progressive MS and that there is a critical temporal window of intervention to delay or prevent this metabolic impairment.

Currently the team is deriving neurons from induced pluripotent stem cells from MS patients and is planning to characterize their mitochondrial function. If successful, the researchers will advance the current knowledge of the progressive forms of MS laying the groundwork for the identification of potential therapeutic targets for progression and potential biomarkers predictive of disease course.

Mobile Brain-Body Imaging of Gait and Cortical Activity

Pierfilippo De Sanctis, PhD, Albert Einstein College of Medicine

MS patients often experience difficulty in walking, which becomes more challenging when paired with a cognitively demanding task such as texting or talking. With support from a FY16 Exploration–Hypothesis Development Award, Dr. De Sanctis has been studying how MS patients with mobility limitations leverage their cognitive resources to most effectively organize their behavior as they ambulate through a complex and ever-changing environment. He is applying the mobile brain/body imaging (MOBI) system to examine changes in gait and cortical activity in response to sensory and cognitive load during dual-task walking. The MOBI system integrates high-density electroencephalogram with three-dimensional motion capture to track kinematics of the head and feet in order to monitor brain activity, gait pattern, and body posture. In a recent *Journal of Neurophysiology* publication, his team utilized the MOBI system on young adults during dual-task walking. During increased sensory load, participants walked with shorter and wider strides indicating a more restrained pattern of gait. Interestingly, simultaneous engagement in a cognitive task attenuated these effects of sensory load on gait.

Dr. De Sanctis will expand this work to include individuals with MS in order to determine the neural underpinnings of sensory-motor dysfunction and increased cognitive-motor interference in MS patients walking under environmentally challenging conditions. These findings provide insight into the neural correlates of gait adaptation and move Dr. De Sanctis and his team closer to potentially discovering objective brain measures to enhance diagnostic and therapeutic assessments of MS.

"The MSRP continues to attract a diverse and excellent set of applications in the key Focus Areas. I was impressed to see the diversity of molecular and pharmacological approaches that are being undertaken to approach the need for new therapies aimed at improving myelin repair and preventing axonal degeneration. Likewise, the novel imaging sequences and other biomarker approaches that are being pursued will likely lead to significant advances in our ability to predict disease outcome in MS. This is a vital step in the successful development of new therapeutics and intelligent trial design as the field focuses more on regeneration and protection rather than immune modulation. The views of the consumer reviewers and scientific panel members were valuable and insightful. I am confident that the support this program provides will drive the field forward in what remains a challenging financial environment."

Fraser Sim, PhD, University at Buffalo, Jacobs School of Medicine and Biomedical Sciences, MSRP Peer Reviewer

Neurofibromatosis Research Program

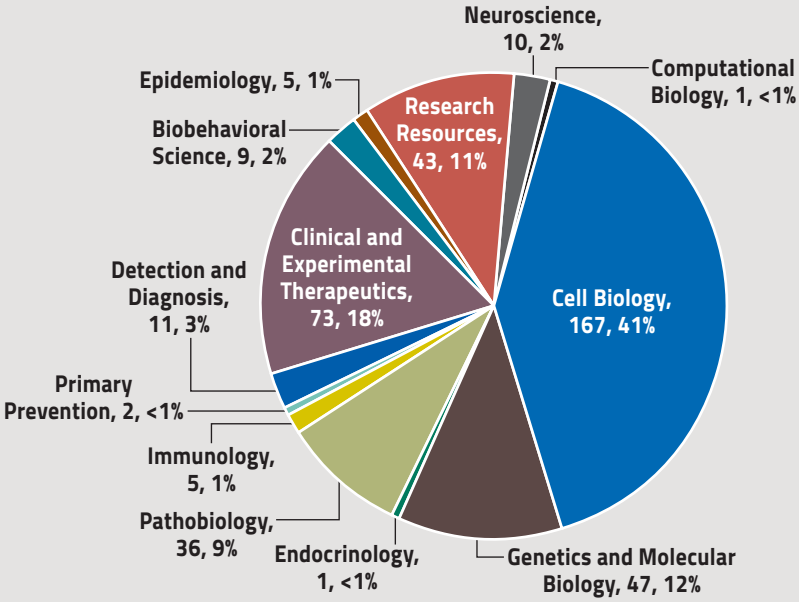
Vision: Decrease the clinical impact of neurofibromatosis

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

Program History

The Neurofibromatosis Research Program (NFRP) was established in FY96 when the efforts of NF advocates led to a congressional appropriation of $8M. Since that time, $347.85M has been appropriated to the program, including $15M in FY19.

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 387 awards spanning basic, clinical, and population-based research.



FY96-FY18 NFRP Portfolio Investment by SCS Code

"As a peer reviewer, I soon realized that my front-lines voice matters. I believe the NFRP is so efficiently run because it is managed by the DOD. It is a results-oriented program with a real return on investment that gives hope to NF patients and their families. I am inspired by the brilliant minds of the scientific community who are working to decrease the clinical impact of NF."

Gregg Erickson, FY18 NFRP Consumer Peer Reviewer

Pathophysiology and Treatment of Muscle Weakness in NF1

Aaron Schindeler, PhD, The Children's Hospital at Westmead

NF1 is a genetic syndrome in which neurofibromin-deficient cells are overactive in the Ras-MEK-ERK signaling pathway, affecting the musculoskeletal system and associated with bone dysplasias, spinal malformations, failure to repair long bones after fracture, muscle weakness, and low muscle tone. Dr. Aaron Schindeler received an FY13 NFRP Exploration - Hypothesis Development Award to investigate whether a MEK inhibitor or dietary changes may also have therapeutic value for the muscular issues of conditional knockout Nf1-/- mice. The skeletal muscle knockout (Nf1MyoD-/-) and limb embryonic tissue knockout (Nf1Prx1-/-) mouse models were used in a study from Dr. Schindeler's group that focused on metabolism and intramyocellular lipids for possible dietary interventions. After 8 weeks on a diet of reduced long-chain fatty acids and increased medium-chained fatty acids with L-carnitine, Nf1Prx1-/- mice showed a 45% increase in grip strength and a 71% decrease in intramyocellular lipid staining compared to their control-diet littermates. Furthermore, protein and histologic analysis of muscle biopsies from six individuals with NF1 confirm the presence of intramyocellular lipids in muscle tissue.

In the most recent study, Dr. Schindeler's team used Nf1MyoD-/- and Nf1Prx1-/- mice to test the capacity of PD0325901, a MEK inhibitor, to influence fat droplets stored in muscle cells. They learned that dosing pregnant mice with PD0325901 could modify the developmental muscle phenotype of the Nf1MyoD-/- mice, but not the Nf1Prx1-/- mice, which supports the idea that the MEK/ERK-dependent mechanism underlies NF1 muscle metabolism during development. Dr. Schindeler's work through the Exploration - Hypothesis Development Award provides strong proof of principle that treatments affecting lipid metabolism will be able to ameliorate the muscle symptoms of NF1, and has yielded important insights into both the mechanisms of disease and novel therapies. There is hope to expand this research into human studies to confirm dietary influence as well as explore other lifestyle factors that may cause NF1 muscle weakness and lipid accumulation. In 2019 Dr. Schindeler's team is commencing a small clinical trial for L-carnitine supplementation in children with NF1 to determine whether this intervention improves quality of life and functional outcomes.

Cerebellopontine Angle (CPA) Model: A Novel Tool for Investigating Immunotherapy in Neurofibromatosis Type 2 Vestibular Schwannomas

Lei Xu, MD, PhD, Massachusetts General Hospital

NF2 is a disorder that is typically inherited and characterized by bilateral vestibular schwannomas (VSs), which are benign nervous system tumors composed of neoplastic Schwann cells. VSs cause progressive hearing loss, which often leads to increased social isolation and higher rates of depression, and in some cases, dizziness, facial paralysis, other neuropathies of the cranium, and even mortality. With support from an FY15 New Investigator Award, Dr. Lei Xu and her team are utilizing animal models to evaluate the potential of immunotherapy in controlling tumor progression for enhanced survival. Preliminary data from Dr. Xu's group confirms the presence of immune checkpoint molecules in NF2 schwannomas and demonstrates that NF2 patients are in an immune suppressive state. Furthermore, anti-VEGF treatment, via normalizing the abnormal schwannoma vasculature, has been shown to improve perfusion, reduces tumor hypoxia and significantly enhances radiation efficacy.

Dr. Xu and her team recently published a protocol on their newly developed CPA model for the in vivo study of NF2-related VSs pathophysiology and neurological function, which describes a technique for delivering schwannoma cells into the mouse brain CPA region. These new techniques could be utilized in elucidating the complex biology of NF2 and VS-associated hearing loss, and the CPA model can also be applied in the study of metastatic lesions, meningiomas, lipomas, and various other CPA disorders. If successful, Dr. Xu's work through the New Investigator Award will fill the current knowledge gap in the biology of the immune component of VSs, inform on the immune status of NF2 patients, and provide knowledge on the potential efficacy of immunotherapy for NF2-related schwannomas. The findings from this group will also determine the rationale and directly inform the design of future clinical trials for combined immunotherapy with anti-VEGF treatment. This effort has the potential to improve treatment of patients with NF2 VSs through rapid translation to the clinic.

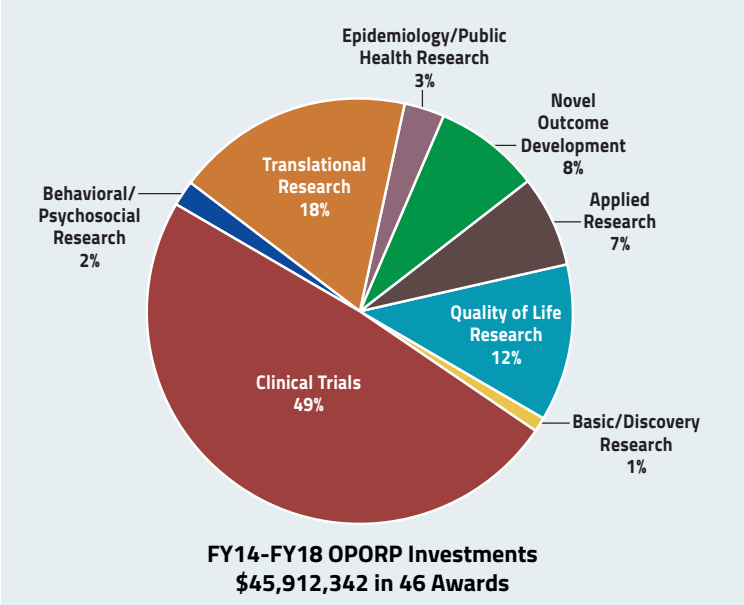
Orthotics and Prosthetics Outcomes Research Program

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

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.



FY14-FY18 OPORP Investments
$45,912,342 in 46 Awards

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 throughout the continuum of care 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.

"Because OPORP values the opinions of the consumer, a combat wounded Veteran like myself is able to participate in the application review process in a meaningful way. This has been an incredible experience for me, as I have been able to provide direct feedback, on behalf of the end user, to the outstanding scientists during Programmatic Review who are solving the difficult problems that affect my friends in the military community."

Tristan Wyatt, OPORP Programmatic Panel Consumer Reviewer

Narrowing Beam-Walking Test for Assessing Fall Risk in Lower-Limb Prosthesis Users

Andrew Sawers, PhD, University of Illinois at Chicago

Dr. Sawers' research focuses on three critical areas related to balance and falls among lower limb prosthesis users: (i) determining who is at risk for a fall (and thus in need of treatment), (ii) diagnosing why someone is at risk for a fall (in order to personalize treatment), and (iii) predicting how at-risk individuals are likely to fall (in order to prioritize treatment). Dr. Sawers and his collaborators are recipients of an FY16 Prosthetics Outcomes Research Award to establish the validity and reliability of the Narrowing Beam Walking Test (NBWT), a novel performance-based balance test. Prior research demonstrated that a challenging balance task, walking along a narrowing beam, has the potential to address limitations present in many balance tests (i.e., they are too easy, have ceiling effects, and have low diagnostic accuracy). Dr. Sawers and his colleagues demonstrated that the NBWT discriminates fallers and non-fallers with greater accuracy than existing balance tests. They have also established key validity and reliability indices, including cut-off thresholds, likelihood ratios, and minimal detectable change values for the studied tests. These indices provide clinicians with much-needed guidance regarding test selection, administration, and interpretation. Importantly, Dr. Sawers' team discovered that accommodating practice effects through test administration and scoring procedures was central to the NBWT's ability to identify fallers from non-fallers. Recently, they found that other balance tests are susceptible to practice effects that may limit these tests' discriminative, evaluative, and predictive abilities. Dr. Sawers' team is currently assessing the predictive validity of the NBWT, developing methods to improve measurement of fall-related events among lower limb prosthesis users, and designing tools to facilitate selection, administration, and interpretation of performance-based tests.

Prosthetic Knee Outcomes in Early Rehabilitation

Sara Morgan, PhD, University of Washington

Dr. Morgan is a prosthetist-orthotist and researcher who aims to optimize health outcomes following limb amputation. As the recipient of an FY16 Prosthetics Outcomes Research Award, Dr. Morgan and her research team are evaluating the effect of different prosthetic knee technologies on function, health, and quality of life following transfemoral amputation. In principle, prosthetic knees with microprocessor control are ideal initial prosthetic knees, as they maximize safety to promote mobility following amputation. Further, these knees normalize gait biomechanics and have the potential to reduce the need for walking aids in early rehabilitation. However, there is a lack of evidence to guide prescription of microprocessor knee technology in the earliest phases of prosthetic rehabilitation. To address this gap, Dr. Morgan and her team are conducting a pilot randomized controlled trial to assess falls, step activity, balance confidence, mobility, health-related quality of life, and community integration of people with recent amputation in two prosthetic knee conditions: a knee with microprocessor control of stance phase and a non-microprocessor knee. Both knee types are clinically available and appropriate for people in early rehabilitation. Study participants are enrolled prior to receiving their first prosthesis and are randomly assigned to knee conditions. Dr. Morgan hypothesizes that use of microprocessor-controlled knees in the early rehabilitation period will result in improved outcomes for people with recent amputation and increase the likelihood of long-term prosthetic use. If supported, evidence produced by this study will help make microprocessor knees available to people early in their post-amputation recovery period.

"Having served on the OPORP programmatic panel for numerous years, I can say, without question, that our panel of civilian, DOD, and VA members is highly dedicated and personally invested in better understanding how orthotic/prosthetic form, fit, and function impacts the rehabilitation and quality of life of our injured Service members. These Service members are at the center of every decision we make. Our ultimate goal is to optimize and enhance their rehabilitation process in order to improve their overall level of function and quality of life, both in the near and far-term. It is critical that we continue to fund top-tier research in order to corroborate best practice patterns and to advance the management of injured Service members throughout every stage of rehabilitation."

MAJ Bradley Ritland, US Army Research Institute of Environmental Medicine, OPORP Programmatic Panel Member

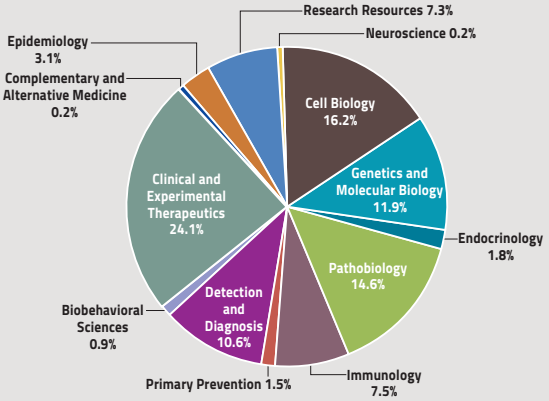
Ovarian Cancer Research Program

Vision: To eliminate ovarian cancer

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

Program History

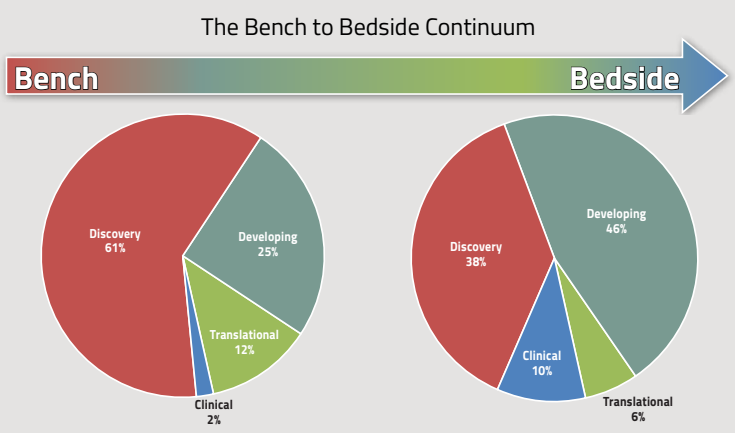
The DOD Ovarian Cancer Research Program (OCRP) was established in 1997 to define and address the critical research gaps facing the ovarian cancer community. The OCRP has defined a strategic plan that highlights the high-impact research goals critical to achieving its vision and mission. With $336.5M in congressional appropriations through FY19, the OCRP is the second-leading funder of ovarian cancer research in the United States. The OCRP has transformed the landscape of ovarian cancer to the benefit of patients everywhere by funding high-impact research in the prevention, screening, diagnosis, and treatment of ovarian cancer as well as survivorship and quality of life issues. Through FY18, the OCRP has funded 453 research awards, resulting in over 1,737 peer-reviewed publications and 110 patent applications. The appropriation for OCRP for FY19 is $20M.



FY97-FY18 OCRP Portfolio Investment by SCS Code

Program Portfolio: Funding Research from Bench to Bedside

The OCRP designed an investment strategy that emphasizes high-impact translational research, innovation, and development of talented early-career investigators who are committed to studying this disease. The OCRP investment strategy portfolio shows the percentage of awards in each research area. Funding is across many scientific areas; however, the largest focus is on therapeutics. The OCRP funds research across the bench-to-bedside continuum as shown. In recent years, there has been increasing emphasis on high-impact clinical research that has immediate benefits to the ovarian cancer patient, as seen when comparing the research in past concluded awards versus currently open awards during FY19.



Concluded Awards During FY19 (320 awards ranging from FY97-FY15)

Current Awards During FY19 (133 awards ranging from FY11-FY18)

Closing the Gaps in Ovarian Cancer Research

The OCRP recognizes gaps in ovarian cancer research and has addressed those shortcomings by funding cutting edge research in these areas. Examples of notable research efforts are listed below.

Metastasis

Metastasis Research:
26 Awards
Over $10M Invested
Resulted in:
40 Publications
3 Patents

Sandra Orsulic, PhD, Cedars-Sinai Medical Center, generated a gene signature that identifies ovarian cancer patients with high risk of metastasis who are unlikely to respond to standard treatment (surgery and chemotherapy) and should be triaged for personalized treatment approaches. Current efforts include optimizing the gene signature and developing an assay for use in the clinical setting.

Ronald Buckanovich, MD, PhD, University of Michigan, determined that a novel antibody was able to restrict ovarian cancer cell growth and inhibit metastasis. This presents a novel therapeutic that could have clinical impact and potentially restrict the highly metastatic disease. This therapeutic is currently under development for first in human clinical trials.

Immunotherapy

Immunotherapy Research:
54 Awards
Over $34M Invested
Resulted in:
135 Publications
8 Patents
6 Clinical Trials

Dmitriy Zamarin, MD, PhD, Sloan Kettering Cancer Center, focuses on the identification of biomarkers of response and resistance to immunotherapies and on the development of novel immunotherapeutic treatment strategies in ovarian cancer. This is critical with advanced disease where an unsuccessful treatment would be fatal. One such strategy, using a combination of ICB with oncolytic viruses, can lead to tumor regressions in animal models. This has led to a Phase II clinical trial for a combination immune treatment for ovarian cancer.

BRCA and Homologous Recombination Mutations

BRCA and HR Research:
46 Awards
Over $37M Invested
Resulted in:
243 Publications
8 Clinical Trials

Elizabeth Swisher, MD, University of Washington, developed a diagnostic sequencing test to detect mutations in BRCA1, BRCA2 and other key homologous recombination (HR) DNA repair genes in tumor tissue (BROCA-HR). This test is being used in many clinical trials to identify the cancers most vulnerable to treatment with specific cancer drugs including patients without BRCA mutations. Data from the associated ARIEL2 clinical trial contributed to FDA approval for the PARP inhibitor rucaparib.

Ovarian Cancer Academy: 10 years of empowering early career ovarian cancer investigators

Academy Facts:
8 Graduates
16 Current members
627 publications
158 funding grants worth over $47M
6 patents

Since FY09, the Ovarian Cancer Academy's highly committed Early-Career Investigators, their mentors, the Academy Dean, and the Assistant Dean have been diligently collaborating and networking as they work toward becoming the next generation of leaders in ovarian cancer research and eliminating ovarian cancer. Their accomplishments span ovarian cancer research areas.

High-Impact Advances Supported by the OCRP

Prevention

- Shared biorepository of clinical data and biospecimens
- Genetic testing guidelines in the US and Australia
- Salpingectomy as a less invasive alternative surgery

Detection

- Falloposcope system to identify ovarian cancer
- Adapting pap smears to detect ovarian cancer
- OPHID/I2D: An online database of protein interactions

Survivorship

- Exercise to reduce the effects of chemo-induced memory problems
- Flaxseed as maintenance therapy for ovarian cancer patients in remission
- Self-administered relaxing acupuncture to reduce fatigue and enhance quality of life
- Initiated two consortia aimed at understanding and enhancing long-term survivorship

Treatment

- Junctional opener 1 triggers the opening of cells, allowing treatment to enter and be more effective
- Accelerated FDA approval for rucaparib treatment in patients with prior chemotherapies and recurrences
- Utilizing heat shock protein inhibitor in combination with PARP inhibitor to treat recurrent ovarian cancer

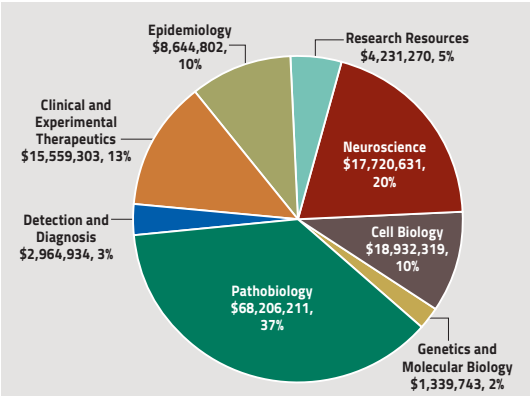
Parkinson's Research Program

Vision: To eliminate Parkinson's disease through research on neurotoxin exposure and treatments 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

Program History

The DOD Parkinson's Research Program (PRP) was established by Congress for research on neurotoxin exposure treatment in those with Parkinson's disease (PD). The PRP was initiated in FY97 and supports Parkinson's research of exceptional scientific merit leading to an understanding of the underlying biologic mechanisms and therapeutic interventions of neuro-degenerative effects caused by deployment, environmental, and occupational exposures. From FY97 through FY18, approximately $436.75M have been appropriated by Congress for this program. The FY19 appropriation is $16M.



FY10-FY18 PRP Portfolio Investment by SCS Code

Military Relevance

Parkinson's is the second most common neurodegenerative disease and is estimated by the VA to affect more than 80,000 Veterans, a proportionately greater rate 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. Significant among these occupational and environmental risk 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; and
- repeated or prolonged disruption of autonomic nervous function.

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

[1] Lorene Nelson, PhD, 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)

Consumer Perspective

J. Sam Erwin, MS, MA, ATR, PRP Consumer Peer Reviewer

I remember the day and the time, September 28, 1999, 1:30 p.m., when the movement disorder specialist gave the diagnosis of PD. It was not a surprise to me since my symptoms of stiffness, pain, and inflammation led me to a rheumatologist at the beginning. The tremor, loss of balance, and dragging footsteps took me across the hall to the movement disorder specialist. A couple of years into living with this diagnosis, I struggled with the lack of knowledge and understanding of how I continue to progress through my life. An invitation led me to my training at the Parkinson's Foundation national Patient Engagement in Research program, Parkinson's Advocates in Research. This program looks for individuals with an interest in research and a willingness to work with researchers. The objectives of being an advocate are to prioritize research, improve studies, and influence stakeholders in research. These objectives became important to me as I continued to attend a variety of events including the CDMRP PRP. As a Veteran and spouse of a Veteran, I recognize the need to expand the knowledge and understanding of the impact the environment has on the Soldier. This led me to several conferences, seminars, and workshops on living with a chronic, progressive disease and introduced me to the many organizations and programs. This is how I was brought to the world of advocacy and the continuation of my education. My presence as a consumer with the Parkinson's Foundation and the CDMRP PRP is not the same as a scientist's, whose knowledge could lead you into the workings of the brain, neurons, and other processes of the body. My presence brings the human factor to the discussion, to remind the stakeholders, scientists, and peer reviewers that these individuals are trained to be strong in duty, yet at times passive in matters of health, when it comes to doing their duty. It is a privilege to sit across the table with individuals impacted by PD and listen to their stories. It is a pleasure to represent them at the research table. I hope to expand the table and the number of individuals I have an opportunity to be with, bringing closure to the gaps present in the communication of information. Thank you for the opportunities given to me to speak with the many legislatures, medical staff, scientists, my peers, and, most importantly, the family members who seek to understand but also to be heard.

Research Highlight

Preventing Parkinson's disease: Identifying Parkinson Disease Before Motor Signs

Alberto Ascherio, MD, PhD, Harvard T.H. Chan School of Public Health

The clinical diagnosis of PD is preceded by years of silent neurodegeneration. When diagnosed, key brain regions have already lost more than half of their dopaminergic neurons. Dr. Alberto Ascherio of the Harvard T.H. Chan School of Public Health initiated a longitudinal investigation in apparently healthy individuals to better understand PD's prodromal signs. The study, funded by the DOD PRP, takes advantage of two unique populations, the Nurses' Health Study (NHS) and the Health Professionals Follow-Up Study (HPFS) with over 150,000 men and women followed since 1976 (NHS) and 1986 (HPFS). The study includes assessments of physical and mental function and biennial questionnaires to assess their diet, physical activity, and medical history, including use of medications. Over the past several years, Dr. Ascherio's team has been able to identify a subset of over 20,000 individuals at higher than average risk of PD and to screen these individuals for probable REM sleep behavior disorder, olfactory loss, diminished color vision, excessive daytime sleepiness, and other characteristics that may indicate prodromal PD. They have also assessed these same features among cohort participants who were recently diagnosed with clinical PD. As reported in their recent publication[3] the features appear to act synergistically – the odds of having clinical PD were over 160-fold higher among individuals with three selected features, and over 1,300-fold higher among those with more than five features. Preliminary findings also showed that individuals who engage in regular physical activity and those who adhere to a Mediterranean diet, are less likely to develop features of prodromal PD. Dr. Ascherio hopes to longitudinally follow the cohort participants, to refine and validate a predictive algorithm for future clinical PD, to obtain a genetic risk score that will complement the phenotypic and behavioral data already collected, and to integrate the prodromal features and genetic risk score with information on established and novel risk factors for PD. He expects to be able to develop an efficient screening strategy for the identification of those who are unknowingly suffering from the progressive neurodegeneration that leads to clinical PD. Such screening would radically improve the possibility of identifying and testing novel neuroprotective treatment and lead to prevention of the disease and treatments for those already suffering PD motor signs.

[3] Hughes K, Gao X, Baker JM, et al. 2018. Non-motor features of Parkinson's disease in a nested case-control study of US men. *J Neuro/Neurosurgery Psychiatry* 89:1288-1295.

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.

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 100 research projects since its inception in FY11 ranging in topics from TBI-AD 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.

Overarching Challenges

Paucity of Research Resources: Lack of resources and models available to translate findings regarding the interrelationship between TBI and subsequent AD/ADRD

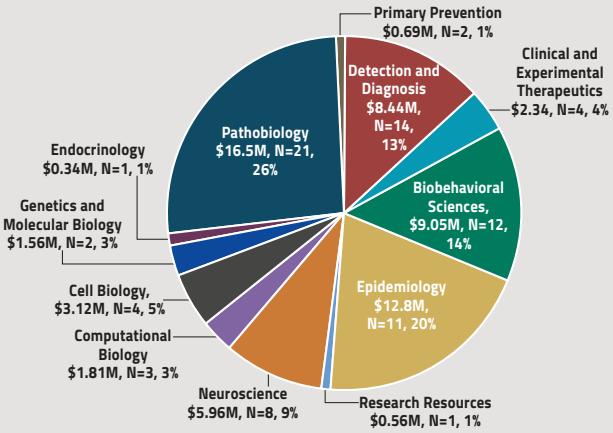
Paucity of Clinical Studies: Lack of clinical studies examining the interrelationship between TBI and subsequent AD/ADRD

Diagnostics and Prognostics: Need for technologies, tests, surveys, questionnaires, devices, biomarkers, or analyses to detect TBI sequelae for AD/ADRD

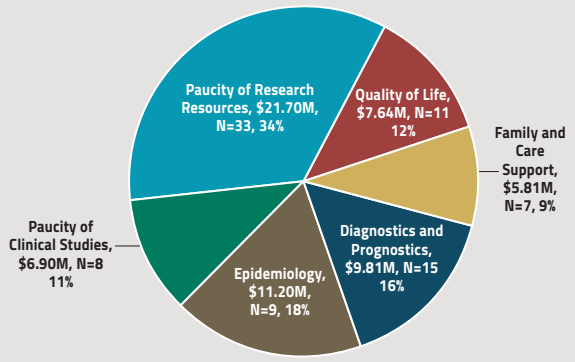
Epidemiology: Lack of epidemiological research to examine the interrelationship between TBI, risk and resiliency factors, and subsequent AD/ADRD

Quality of Life: Need for technologies, assessments, interventions, or devices to benefit individuals living with the common symptoms of TBI and AD/ADRD

Family and Care Support: 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 AD/ADRD



FY14-FY18 PRARP Portfolio Investment by SCS Code



FY14-FY18 PRARP Overarching Challenge Investments

Providing Support in Real Time with Smart Technologies to Improve Quality of Life

Maureen Schmitter-Edgecombe, PhD, Washington State University

Individuals with dementia, mild cognitive impairments, or TBIs all face similar challenges. These include memory disorders, depression, and executive functioning deficits. All of these can impact an individual's ability to live an active and full life on a daily basis. Technologies that enable a person's ability to compensate for these deficits benefit not only the individual, but also his/her caregiver. These technologies can allow an individual to live at home or perhaps assist in recovery from a TBI.

Dr. Maureen Schmitter-Edgecombe is studying a novel combination of technologies to allow individuals to maintain functional independence. She is exploring a combination of a digital memory notebook and smart home technologies. The combination is thought to ensure that individuals with cognitive or executive functioning deficits will be able to complete daily tasks with minimal assistance. This tool may also reduce the amount of assistance needed from caregivers, who may be faced with caring for others in their households. This potentially boosts quality of life for the individual living with the impairment as well as that person's caregiver. Dr. Schmitter-Edgecombe and her team have refined the prototype for their notebook based on feedback from 28 study participants. The cohort included TBI, caregivers, and individuals diagnosed with mild cognitive impairment. The feedback considered overall satisfaction with the tool, the tool's interface, and ease of use. User feedback significantly and positively influenced the design of the notebook. Preliminary data also indicates that the digital notebook is easy to learn to use, even for those with cognitive impairment and little familiarity with technology. Dr. Schmitter-Edgecombe and her team have integrated the notebook with smart home technologies. The smart home technologies recognize and automatically add to the notebook activities the resident completes (e.g., preparing meal, medications) and prompt notebook use at opportune times (e.g., when transitioning between activities).

Detection of Amyloid-Beta and Tau Misfolded Oligomers in Biological Fluids of TBI and AD Patients

Claudio Soto, PhD, University of Texas Health Science Center at Houston

AD and its related dementias are a family of elusive diseases with no known treatment. There are a variety of suspected risk factors that promote the pathogenesis of AD, including TBIs. Two proteins, amyloid and Tau, are well-known biological hallmarks of AD. All ADRDs show different protein pathologies, but all result in similar clinical symptoms regarded as dementia. These symptoms may involve cognitive deficits and mental health challenges.

Despite more than a century since the discovery of AD, autopsy is still the gold standard confirmation for ADRDs. Many individuals who receive a clinical dementia diagnosis will never know whether they indeed have AD or the severity of their condition or how fast it will progress. Radiotracers specific to amyloid and Tau are now available, but they are costly and require robust analyses by trained scientists. Diagnostics that are capable of safely, cheaply, and specifically diagnosing the development of amyloid and Tau pathology reflect a current gap in both TBI and dementia care.

All of the protein pathologies that comprise ADRDs go through a process of "clumping" or oligmerization ahead of forming larger, microscopic structures such as an amyloid plaques or Tau tangles. Dr. Claudio Soto is studying how TBI leads to oligomerization of amyloid, Tau, and α-synuclein. Syn is another protein that aggregates in the human brain leading to Lewy body dementia or PD. Dr. Soto's tests don't require complex radiotracer diagnoses. Instead, his tests use blood or cerebrospinal fluid. At the heart of his studies is a technology called protein misfolding cyclic amplification (PMCA). PMCA amplifies a pathological signal from misfolded amyloid, Tau or Syn in blood or cerebrospinal fluid enabling their detection. Preliminary data have shown that the test has both high specificity and sensitivity for amyloid, Tau and α-synuclein species. The work currently awaits human validation, which will be funded under this grant.

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

Lucien Richardson, Alzheimer's Association

Peer Reviewed Cancer Research Program

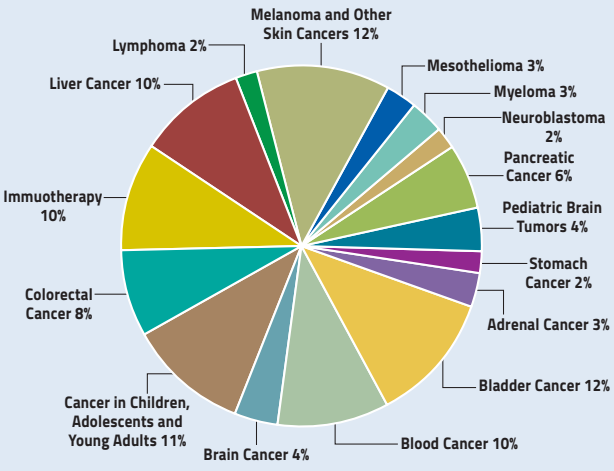
Vision: To advance mission readiness of US military members affected by cancer and to improve quality of life by decreasing the burden of cancer on Service members, their families, and the American public

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

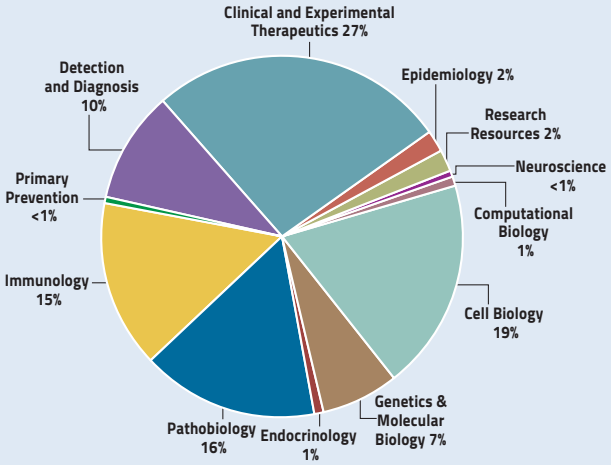
FY19 Military Health Focus Areas
Environmental/exposure risk factors associated with cancer
Gaps in cancer prevention, early detection/diagnosis, prognosis, treatment, and/or survivorship that may impact mission readiness and the health and well-being of military members, Veterans, their beneficiaries, and the general public

Program History

The Peer Reviewed Cancer Research Program (PRCRP) was established in FY09 to support innovative research in cancers and other specialty areas specifically designated by Congress as relevant to Service members and families. From FY09 through FY19, Congress has appropriated $429.8M to PRCRP, which in turn has invested in cancer research covering 25 topic areas.* PRCRP-funded research has advanced knowledge in the prevention, early detection, diagnosis, and treatment of cancer that benefits Service members, their families, and the American public. As a research funding program, the PRCRP crafts its investment strategy around the requirement to be relevant to military health concerns. All applications submitted to and funded by the PRCRP must show relevance to military health. In FY19, there are two military health Focus Areas. Over the past 10 years, PRCRP has employed a variety of funding mechanisms to address military health.



FY18 PRCRP Portfolio Investment by Topic Area (% Research Dollars)



FY09-FY18 PRCRP Portfolio Investment by SCS Code* (% Research Dollars)

* As of publication, the FY19 applications were under review.

PRCRP Funded Research Through the Cancer Care Spectrum

Biology/Etiology

Helicobacter pylori-Induced DNA Double-Strand Breaks and Gastric Cancer; Douglass Merrell, PhD, Uniformed Services University of the Health Sciences; **Topic Area: Stomach Cancer**

Supported by an FY17 Idea Award with Special Focus, Dr. Merrell is investigating how *Helicobacter pylori (H. pylori)* infection damages DNA and leads to development of gastric cancer. The study proposes to find out if *H. pylori* causes the formation of R loop structures in DNA. Additionally, he wants to know if blocking R loops will eliminate tumor development.

Prevention

The Association Between Molecular Markers in Colorectal Sessile Serrated Polyps and Colorectal Cancer Risk; Andrea Burnett-Hartman, MPH, PhD, Kaiser Foundation Research Institute; **Topic Area: Colorectal Cancer**

Sessile Serrated Polyps (SSPs) increase the risk of developing colorectal cancer, but very little is known about why some patients with SSPs develop colon cancer and others do not. With an FY14 Career Development Award, Dr. Burnett-Hartman has analyzed SSPs for biomarkers and unique abnormalities that can be used to predict whether a polyp has an increased risk of developing into cancer.

Diagnosis/Detection

Abbreviated Magnetic Resonance Imaging and Biomarker-Based Detection of Early Liver Cancer; CDR Robert Marks, MD, Naval Medical Center, San Diego; Claude Sirlin, MD, University of California, San Diego; and Rohit Loomba, MD, University of California, San Diego; **Topic Area: Liver Cancer**

Funded by an FY17 Translational Team Science Award, the scientific team led by CDR Marks and Drs. Sirlin and Loomba aim to develop a more accurate and cost-effective abbreviated Magnetic Resonance Imaging-based surveillance strategy for individuals at risk for developing hepatocellular carcinoma (HCC). This screening method could potentially lead to earlier detection of HCC in patients with chronic liver disease, thus leading to potentially improved treatment outcomes.

Prognosis

Mechanisms of Resistance to Immunotherapy in Osteosarcoma; Jaime Modiano, VMD, PhD, University of Minnesota, Twin Cities; **Topic Area: Cancer in Children, Adolescents, and Young Adults**

Challenges to immunotherapy, such as resistance to ICB, affect the prognosis for osteosarcoma patients. Dr. Modiano proposed, in a FY17 Idea Award with Special Focus, to identify mechanisms to circumvent this resistance. If successful, Dr. Modiano's work could potentially result in methods, not only to overcome immunotherapy resistance, but to personalize therapy options and improve prognostic outcomes for osteosarcoma patients.

Treatment

Rational Engineering of Designer Nanoparticles to Target Multiple Myeloma; Zihni Bilgicer, PhD, University of Notre Dame; **Topic Area: Blood Cancers**

With an FY14 Career Development Award, Dr. Bilgicer identified unique cell-surface receptors on Multiple Myeloma (MM) cells to differentiate healthy cells from MM. Dr. Bilgicer proposed to combine nanoparticles, for enhanced drug delivery, with synergistic drug combinations (i.e., Bortezomib, a therapeutic that reverses MM cells resistance to cell death) and to test this system in an animal model. The results indicated that the nanoparticles guided the chemotherapeutics directly to the MM cells, improving drug delivery and treatment success.

Survivorship

Towards Precision Prevention: Testing a Novel Risk Prediction Algorithm in Pancreatic Cancer; Shannon Lynch, PhD, The Research Institute of Fox Chase Cancer Center; **Topic Area: Pancreatic Cancer**

With an FY16 Career Development Award, Dr. Lynch is using machine-learning to evaluate pancreatic cancer risk factors with hopes of developing new prediction models for development of this disease. Dr. Lynch analyzed a wide variety of genetic, molecular, environmental, nutritional, and biomedical risk factors in order to identify the best combination of predictors for pancreatic risk and survival. Results from this study could be used to identify high-risk individuals and improve pancreatic cancer intervention strategies.

Peer Reviewed Medical Research Program

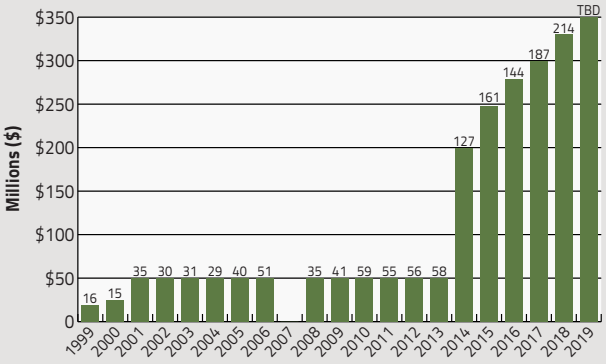
Vision: Improve the health, care, and well-being of all Military Service members, Veterans, and beneficiaries

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

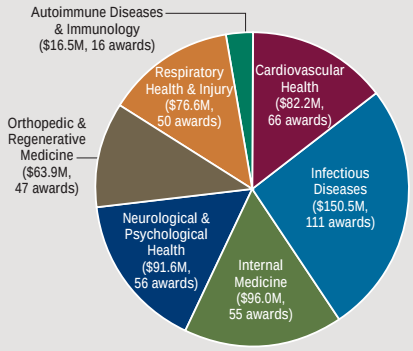
Program History

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, retirees, and their family members. Through its 20-year history, Congress has appropriated $2.35B to the program, which has supported more than 1,385 research awards in 161 unique diseases and conditions, resulting in over 2,700 peer-reviewed publications and 243 patent applications and patents granted. The FY19 congressional appropriation is $350M to solicit research applications in 49 different diseases and conditions.

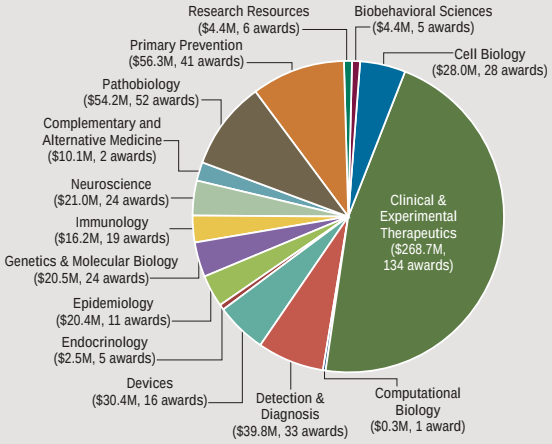
Research supported by the PRMRP to address near-term needs continues a long tradition of research relevant to military health in response to wartime needs that ultimately benefits Service members and civilians alike. Service members, their dependents, military retirees, and Veterans receive military 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. 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, infectious diseases, internal medicine, neurological and psychological health, orthopedic and regenerative medicine, and respiratory health and injury.



PRMRP Appropriations FY99-FY19.
Number of awards made each FY is noted above each bar



FY17-FY18 PRMRP Funding by Portfolio
(% Total Funding). Total Funding $577.3M, 401 awards



FY17-FY18 PRMRP Portfolio Investment by SCS Code
(Total Funding). Total Funding $577.3M, 401 awards

Autoimmune Diseases and Immunology

FY17-FY19 Awards by Primary and Secondary Topic Areas

Arthritis	FY17 (4), FY18 (2), FY19
Guillain-Barre Syndrome	FY17 (1), FY18 (0), FY19
Hereditary Angioedema	FY17 (0), FY18 (0), FY19
Immunomonitoring of Intestinal Transplants	FY17 (0), FY18 (3), FY19
Inflammatory Bowel Diseases	FY17 (4), FY18 (6), FY19
Rheumatoid Arthritis	FY17 (1), FY18 (1), FY19
Scleroderma	FY17 (3), FY18 (0), FY19

Highlights:

Rheumatoid Arthritis

While Rheumatoid arthritis (RA) is an autoimmune disease of the joints, not all patients' symptoms are alleviated by immunosuppressing drugs. One new idea is to directly target fibroblast-like synoviocyte cells that overpopulate, leading to a pro-inflammatory environment in RA joints. Dr. Nunzio Bottini has been able to develop a decoy biologic that can disrupt the interaction that otherwise encourages fibroblast-like synoviocyte aggressiveness, and plans to combine his decoy biologic with currently available immune-targeted treatments to improve RA care and achieve remission.

Inflammatory Bowel Diseases

Drs. David Binion and Claudia Ramos Rivers has developed a prototype computer-based risk prediction platform for patients suffering from Inflammatory Bowel Disease. The multi-faceted prototype aims to help patients and physicians identify the likely disease progression and responses to therapy for a more personal treatment plan. The team has discovered two novel genes associated with severe Inflammatory Bowel Disease. Further optimization and refinement is ongoing, including future plans to incorporate genetic factors of outcomes (pain, narcotic use, etc.).

Infectious Diseases

FY17-FY19 Awards by Primary and Secondary Topic Areas

Antimicrobial Resistance	FY17 (22), FY18 (16), FY19
Diarrheal Diseases	FY17 (8)
Emerging Infectious Diseases	FY17 (19), FY18 (19), FY19
Hepatitis B	FY19
Hepatitis B and C	FY17 (3) & FY18 (3)
Influenza	FY17 (8)
Malaria	FY17 (5) & FY18 (6)
Pathogen-Inactivated Blood Products	FY18 (1) & FY19
Pathogen-Inactivated Dried Cryoprecipitate	FY17 (0)
Tuberculosis	FY17 (8), FY18 (4), FY19
Vaccine Development for Infectious Disease	FY17 (14) & FY18 (26)

Highlights:

Antimicrobial Resistance

MeMed Diagnostics is developing a rapid and accurate host-based test which differentiates between bacterial and viral infections using a compact, user friendly platform for performing the test at the point of care. The development of this platform is a multiagency effort supported by PRMRP, Medical Countermeasure Systems, and the Defense Threat Reduction Agency.

Pathogen-Inactivated Blood Products

To eliminate the risks of whole blood transfusion in theatre (risks of infectious diseases and white blood cells transmission that can trigger immune responses in the recipient), Terumo BCT Biotechnologies developed the Mirasol Pathogen Reduction Technology System (MPRTS) that uses riboflavin and UV-light to inactivate pathogens and white blood cells. This group optimized the existing MPRTS, improving the screening process by reducing the whole blood treatment time in half. Further improvements in mixing system, bag geometry, transportability, and disposability in theatre is ongoing. In addition this group is validating and optimizing the MPRTS by elucidating the molecular mechanism by which viruses (including RNA viruses), bacteria, parasites, and white blood cells would be most effectively inactivated.

Continued on the next 2 pages

Cardiovascular Health

FY17-FY19 Awards by Primary and Secondary Topic Areas

Cardiomyopathy	FY18 (15), FY19
Congenital Heart Disease	FY17 (7), FY18 (7), FY19
Diabetes	FY17 (18), FY18 (19), FY19
Vascular Malformations	FY17 (3), FY18 (3), FY19
Women's Heart Disease	FY17 (9), FY18 (2), FY19

Highlights:

Women's Heart Disease

Dr. Carl Pepine and colleagues at the University of Florida are conducting a Phase III multisite clinical trial to assess whether an aggressive medication regimen will modify risk factors and reduce the likelihood of death in women with coronary arteries having no severe obstruction but with cardiac symptoms and abnormal stress test results.

Congenital Heart Disease

Dr. Lynn Sleeper and colleagues at the Children's Hospital, Boston are conducting a Phase III randomized, multi-center clinical trial of a novel immunosuppression regimen (everolimus and low-dose tacrolimus) as an anti-rejection medicine for pediatric heart transplant patients to reduce or prevent complications of transplant and improve the longevity of the transplanted heart.

Orthopedic and Regenerative Medicine

FY17-FY19 Awards by Primary and Secondary Topic Areas

Musculoskeletal Disorders	FY17 (9), FY18 (9), FY19
Myotonic Dystrophy	FY18 (3), FY19
Nanomaterials for Bone Regeneration	FY17 (6), FY19
Post-Traumatic Osteoarthritis	FY17 (11), FY18 (11), FY19
Pressure Ulcers	FY18 (3), FY19
Tissue Regeneration	FY18 (21), FY19

Highlights:

Musculoskeletal Disorders

Dr. Leonid Bunegin and collaborators at the US Air Force 59th Medical Wing and the USAISR are developing a platform to extend the viability of vascularized tissue. The Universal Limb Stasis System for Extended Storage (ULiSSES) is intended to be an inexpensive, disposable, and field-deployable technology that cools and oxygenates vascularized tissue while filtering out pathogens. ULiSSES will be used to preserve a severed limb and improve outcomes after replantation, potentially avoiding the need for transplantation or prostheses.

Pressure Ulcers

Dr. Robert Chang and his team at the Stevens Institute of Technology are developing technology for the rapid and scalable production of stem cell-based dermal grafts to better treat pressure ulcers. This team is optimizing the fabrication of 3D printed stem cell substrates that will enable scalable production of homogenous stem cell populations, a significant limitation of current stem cell therapies, and development of a better dermal graft to improve chronic wound care.

Respiratory Health and Injury

FY17-FY19 Awards by Primary and Secondary Topic Areas

Acute Lung Injury	FY17 (12), FY18 (9), FY19
Burn Pit Exposure	FY17 (2), FY18 (2), FY19
Constrictive Bronchiolitis	FY17 (0), FY18 (2), FY19
Early Trauma Thermal Regulation	FY17 (0)
Hemorrhage Control	New in FY19
Lung Injury	FY18 (10), FY19
Metals Toxicology	FY17 (2), FY18 (1), FY19
Pulmonary Fibrosis	FY17 (7), FY18 (9), FY19
Respiratory Health	FY17 (11), FY18 (18), FY19

Highlights:

Burn Pit Exposure

Dr. David Savitz and his team at Brown University are conducting a health outcomes study to determine if inhalational exposure to open burn pits during deployment to Afghanistan and Iraq resulted in increased risk of developing respiratory and cardiovascular disease among Veterans.

Lung Injury

Dr. Venkatasivasaisujith Sajja at Walter Reed Army Institute of Research and Dr. Drew Helmer at the Veterans Biomedical Research Institute are examining the effects of blast overpressure lung injury among previously deployed military members. This joint VA/Army research team is investigating the mechanisms underlying the pathogenesis of chronic pulmonary disease after exposure to blasts (e.g., IED explosions) in a rat model of single and repeated blast exposures, which will allow in the long-term, development of countermeasures and therapies to prevent or treat these injuries.

Internal Medicine

FY17-FY19 Awards by Primary and Secondary Topic Areas

Eating Disorders	FY17 (3), FY18 (7), FY19
Endometriosis	FY18 (9)
Epidermolysis Bullosa	FY17 (4), FY18 (1), FY19
Focal Segmental Glomerulosclerosis	FY17 (2), FY18 (5), FY19
Integrative Medicine	FY17 (0)
Interstitial Cystitis	FY17 (2), FY18 (2), FY19
Mitochondrial Disease	FY17 (5), FY18 (5), FY19
Nutrition Optimization	FY18 (1), FY19
Pancreatitis	FY17 (3), FY18 (6), FY19
Polycystic Kidney Disease	FY17 (2), FY19
Sustained-Release Drug Delivery	FY17 (5), FY18 (4)

Highlights:

Eating Disorders

Military Veterans may be particularly vulnerable to the comorbidities associated with eating disorders, such as PTSD, depression, and alcohol and substance use disorders. Dr. Karen Mitchell at Boston VA Research Institute, Inc., and Dr. Zafra Cooper at Yale University are investigating the prevalence of eating disorders among Veterans, as well as the risk factors and potential mental health comorbidities associated with these conditions. The investigators are conducting a cross-sectional study of post-9/11 military Veterans to identify vulnerable subgroups in the hopes of providing insight to clinicians for developing effective and targeted screening strategies.

Mitochondrial Disease

Dr. John Kheir is developing a device that uses a spectroscopic technique to detect efficiency of oxygen delivery within an individual. Successful development of this tool could monitor oxygen delivery in hemorrhagic patients, predict cardiac or organ injury, and determine resuscitation need.

Neurologic and Psychological Health

FY17-FY19 Awards by Primary and Secondary Topic Areas

Cerebellar Ataxia	FY18 (2), FY19
Chronic Migraine and Post-Traumatic Headaches	FY17 (5), FY18 (2), FY19
Chronic Pain Management	FY18 (12)
Dystonia	FY17 (3), FY18 (5), FY19
Fragile X Syndrome	FY17 (2), FY18 (2)
Frontotemporal Degeneration	FY18 (4), FY19
Hydrocephalus	FY17 (2), FY18 (0), FY19
Non-Opioid Pain Management	FY17 (7), FY18 (4)
Resilience Training	New in FY19
Rett Syndrome	FY17 (1), FY18 (2), FY19
Sleep Disorders	FY17 (5), FY18 (3), FY19
Spinal Muscular Atrophy	FY17 (2), FY18 (0), FY19
Tinnitus	FY17 (2), FY18 (2), FY19

Highlights:

Chronic Pain Management

Transplantation of genetically engineered GABAergic neuronal cells may restore the antinociceptive potential of the spinal cord by replacing dysfunctional interneurons, thereby alleviating chronic pain due to migraines or other neurological conditions. Dr. Stanislava Jergova of University of Miami, Coral Gables received an FY18 PRMRP Discovery Award to evaluate intraspinal injection of recombinant GABAergic cells producing MVIIA, an N-type calcium channel blocker that is FDA approved to treat severe pain, to substantially reduce chronic neuropathic pain. Dr. Jergova plans to test this cell-based approach in animal models by measuring the release of analgesic peptides and observing pain-related behavior. If effective, similar methods could be used for alleviating chronic pain syndromes, such as phantom limb pain or chronic headaches, in Veterans.

Sleep Disorders

Dr. Anne Richards and colleagues at the Northern California Institute for Research and Education and the San Francisco VA Medical Center are studying alpha-1 blockers, a class of FDA-approved drugs, in a new indication: to treat nightmare symptoms and other nighttime symptoms of post-traumatic stress in male and female Veterans. In a randomized, double-blind, placebo-controlled clinical trial , this team will better define the efficacy of the alpha-1 blocker doxazosin, an FDA-approved medication, to alleviate symptoms of post-traumatic stress nightmares, sleep disturbances, depression, sexual health, and overall quality of life.

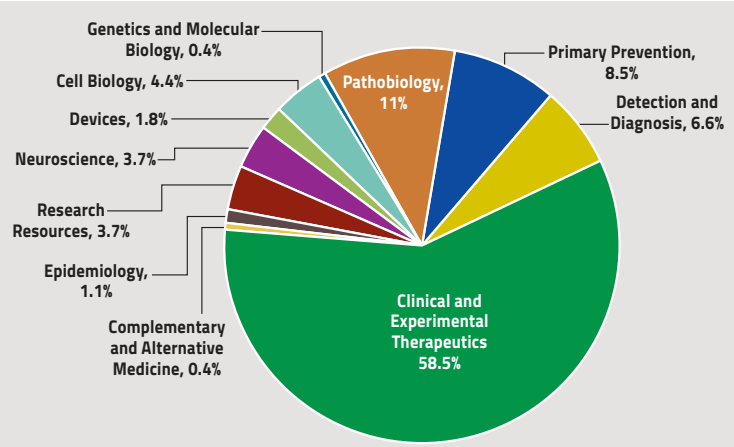
Peer Reviewed Orthopaedic Research Program

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

Program History

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]



FY09-FY18 PRORP Portfolio Investment by SCS Code

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 DOD Peer Reviewed Orthopaedic Research Program (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.

Since its inception in 2009, the PRORP has dedicated its congressional appropriations, totaling $398.5M, 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 255 projects (with an additional 16 awards planned by 30 September 2019) that have focused research on orthopaedic topics including prevention, treatment, rehabilitation, and prosthetics/orthotics.

[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/Govern/Federal/CapHill/Numbers.pdf

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

[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: S1-7.

FDA-Cleared Peripheral Nerve Stimulation System Provides Significant Pain Relief and Reduces Opioid Use

Joseph Boggs, PhD, SPR Therapeutics, Inc. (A Portfolio Company of NDI Medical, LLC)

Many Service members suffer from moderate to severe post-amputation pain that can lead to long-term morbidity, decreased quality of life, and prevent return to maximum function and optimal fitness. Peripheral nerve stimulation (PNS) is a promising non-opioid approach to pain management, but PNS systems have traditionally been limited by lead migration and the invasiveness of device implantation surgeries. With support from an FY11 PRORP Clinical Trial Award, Dr. Joseph Boggs directed a Phase II study on the safety and effectiveness of a novel percutaneous PNS treatment for post-amputation pain (SPRINT® PNS System, SPR Therapeutics, Inc., Cleveland, OH, https://sprintpns.com) designed to reduce the risk of complications and enable delivery of stimulation without surgery. The system is the first and only FDA-cleared PNS system to treat chronic and acute pain. The therapy involves the implantation of a coiled lead constructed of fine wire approximately the size of a human hair. The lead is implanted through a needle-based introducer to target one or more peripheral nerves. The leads are connected to a small, external, wearable pulse generator to provide up to 60 days of stimulation therapy. Both implantation and withdrawal of the leads can be done as a non-surgical outpatient procedure. The study successfully achieved its goal of demonstrating clinically and statistically significant pain relief that was sustained long-term, with no serious or unanticipated study-related adverse events.

TMR Research Drives Change in Standard of Care Practice at WRNMMC

Gregory Dumanian, MD, Northwestern University

Targeted muscle reinnervation (TMR) is a surgical procedure that was first designed and performed to improve the control of advanced prosthetic devices that would utilize the electrical properties of the body's own muscle tissues. Interestingly, patients that underwent the TMR procedure reported significantly decreased pain as a result of the surgical intervention. TMR gives the amputated nerves somewhere to go and something to do—a strategy completely different than the multiple surgery techniques that try to hide the end of the painful nerve.

In 2013, the PRORP funded a clinical trial led by Dr. Dumanian (Northwestern University) and others to investigate the positive side effect; the use of the TMR surgical intervention as a treatment for painful neuromas and phantom limb pain associated with major limb amputation. Walter Reed National Military Medical Center (WRNMMC) was included as a clinical research site, along with others, on the study. Patients who underwent TMR described such a significant reduction in pain that news quickly spread within the amputee patient and care provider populations. The results of the study, which were published in 2019 in both the Journal of the American College of Surgeons and the Annals of Surgery, have provided the clinical evidence to support integration into clinical practice. In 2019, the PRORP learned that TMR is now the standard of care/preferred technique for all non-vasculopathic and non-diabetes-related amputations at WRNMMC at both the time of initial amputation AND for amputees who present with neuroma or persistent phantom limb pain later. PRORP-supported training courses led by the research team will enable the investigators to train surgeons around the country in this technique.

"I really enjoy my time as a PRORP Programmatic Panel member. It allows me to stay involved with cutting-edge research that will positively affect future wounded Warfighters, as well as have an impact on civilian trauma and orthopedic practices. The research funded through the PRORP positively affects both military and civilian orthopaedic treatment."

Matt Anderson, PRORP Consumer, Programmatic Panel Member

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 22-year history of congressional support totaling nearly $1.82B, the 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 ethnic 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.

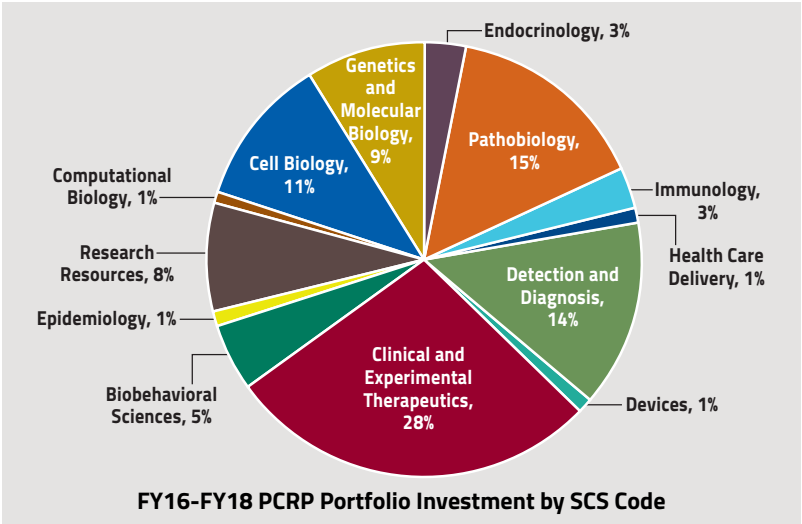
Overarching Strategic Goals

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. The plan includes four overarching strategic goals for providing further advancements that will impact current and future prostate cancer patients. All applications are required to address one or more of the programmatic goals.

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

Program Portfolio

The PCRP strives to diversify its research portfolio with different scientific approaches, ultimately focused on addressing the critical needs of prostate cancer patients. Supported projects range from innovative, exploratory studies to larger projects focused on transforming prostate cancer clinical care.



FY16-FY18 PCRP Portfolio Investment by SCS Code

PCRP Funding Facilitates Development and Translation of Biomarker Assays

Andrew Armstrong, MD, Duke University

The PCCTC recently supported a prospective, multicenter clinical trial, known as PROPHECY, in order to validate two PCRP-funded biomarker assays that detect androgen receptor splice variant 7 (AR-V7) in circulating tumor cells. The PROPHECY trial, led by Dr. Andrew Armstrong at Duke University, consisted of 118 high-risk metastatic castration resistant prostate cancer (mCRPC) patients and showed that AR-V7 detection by both assays was independently associated with shorter progression-free survival and overall survival. AR-V7 was strongly associated with hormonal therapy resistance, suggesting that mCRPC patients with a detectable AR-V7 should potentially be treated with alternative therapies (i.e., taxane or investigational). Conversely, men without detectable AR-V7 had a much greater probability of PSA decline and radiographic responses, highlighting the utility of the assay for making personalized treatment decisions. While work is ongoing, the PCRP was instrumental in providing early funding for the development of both AR-V7 assays, and the PCRP-funded PCCTC was leveraged to help validate the clinical utility of these assays at an unmatched rate. All of these efforts will ultimately help to better inform critical and costly personalized treatment decisions for prostate cancer patients to potentially improve mCRPC patient survival and quality of life.

Highlights

Michael Yu, PhD, (left) University of Utah; and Martin Pomper, MD, PhD, (right) Johns Hopkins University

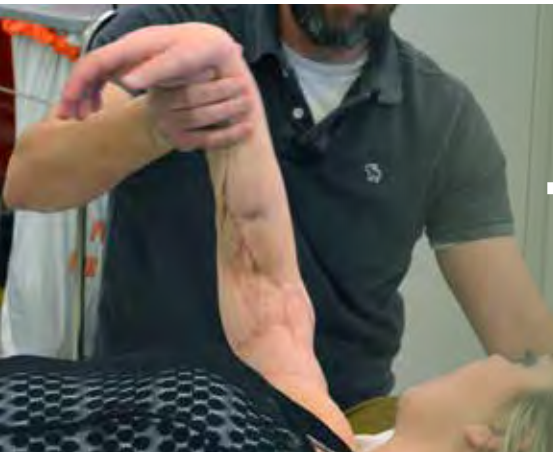
With support from an FY11 Synergistic Idea Development Award, Drs. Michael Yu and Martin Pomper have discovered a novel way of identifying aggressive prostate cancer by looking at the environment surrounding the tumor cell instead of the tumor cell itself. They discovered that collagen hybridizing peptide (CHP) has an affinity to denatured collagen, which is found in the microenvironment of cancer cells that have begun to invade surrounding tissues. Drs. Yu and Pomper are currently developing a novel method for detecting damaged collagens that could be used not only for detecting aggressive tumors, but also for drug delivery. To date, they have successfully imaged invasive cancer in an animal model using fluorescent CHP and are working to develop new strategies for utilizing CHP as a positron emission tomography and magnetic resonance imaging agent. They hope that their research will help newly diagnosed prostate cancer patients make the appropriate treatment decisions depending on the aggressiveness of their disease. CHP has been commercialized for research use, which will better enable further research efforts.

David Rickman, PhD, (left) Weill Medical College of Cornell University; and Himisha Beltran, MD, (right) Dana Farber Cancer Institute

Cancer patients that develop neuroendocrine prostate cancer (NEPC) generally exhibit tumor loss of androgen receptor (AR) expression and acquisition of other unique molecular changes, leading to resistance to AR targeted therapies and poor patient outcomes. Drs. David Rickman and Himisha Beltran have spent the last 10 years researching the molecular characterization and drivers of NEPC, and with funding from an FY17 Impact Award, their team investigated the clinical relevance of their findings and concluded that there is a correlation between N-Myc expression and poor clinical outcome, driven by an interplay of AR and N-Myc signaling. Using complex integrative analysis, the team identified a lineage switch of prostate cancer cells towards a neural identity via epigenetic reprogramming, resulting in cells which favor AR independence and NEPC. Understanding these mechanisms has allowed the team to identify new therapeutic targets such as the N-Myc/Aurora A pathway and epigenetic modifiers such as EZH2 (Enhancer of Zeste Homolog 2). They are continuing their important work to fully or partially reverse the transformation to NEPC to improve treatment options and outcomes for patients with this aggressive form of prostate cancer.

"Reading research proposals and meeting the brilliant scientists in the review meetings removed all doubt that these folks are serious about finding cures. It is not looking for small steps, palliative or chronic regimens. These funds go to giant leaps in knowledge toward significant treatment improvements and cures with sensitivity and compassion for consumers."

Darrell Wilson, Consumer Peer Reviewer, Living with Advanced Prostate Cancer, Awareness Activist and Leader of Two "Us TOO" Prostate Cancer Support Groups



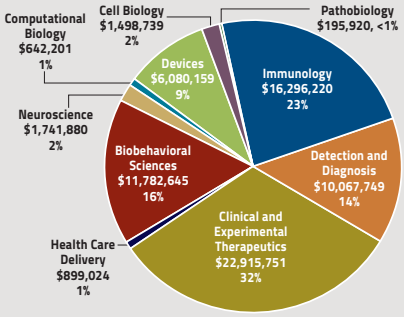
Reconstructive Transplant Research Program

Vision: Making reconstructive transplantation a common reality

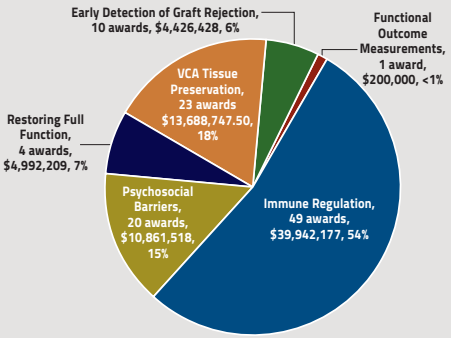
Mission: Optimize form, function, appearance, and psychosocial health for catastrophically injured Service members, Veterans, and American civilians through the development of effective reconstructive transplantation solutions

Program History

The Reconstructive Transplant Research Program (RTRP) was established in FY12 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. The RTRP challenges the scientific community to design innovative research that will foster new directions for and address neglected issues in the field of reconstructive transplantation, specifically vascularized composite allotransplantation (VCA)-focused research. The RTRP has received $93M in appropriations though FY19.



FY12-FY18 RTRP Portfolio Investment by SCS Code



FY12-FY18 RTRP Portfolio Investments by Barrier

FY19 RTRP Focus Areas

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 these 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

Define/assess the benefit or value of VCA, which may include but is not limited to the following:

- Determine the relative value of VCA compared to other treatment options
- Determine how VCA benefits the recipient's communication and interactions with family, friends, workplace, and the community, as well as their individual sense of self

Develop or adapt existing quality of life measures for face transplant recipients

Determine how psychosocial functioning changes over time within VCA recipients

Developing Therapeutic Reagents to Accelerate the Rate of Peripheral Nerve Growth After Reconstructive Transplantation

Samantha J. Butler, PhD, University of California, Los Angeles

Two of the most critical factors contributing to VCA success are: graft acceptance by the recipient's immune system and regeneration of peripheral nerves to reinnervate the transplanted graft. However, little is known about how the required immune suppression effects nerve regeneration and reinnervation of the graft. Dr. Butler and her team received an FY15 RTRP Idea Discovery Award to investigate the effects of several different immunosuppressants on nerve regeneration in a mouse model.

Following surgical nerve transection, mice were treated with either FK506, cyclosporinA [CsA], or rapamycin, and nerve regeneration was assessed by immunofluorescence. After 7 days of recovery post-nerve transection, quantification of GAP43, whose expression increases during regenerative axon growth, revealed that CsA treatment improved regenerative growth by an average of 30%. At this same time point, FK506 and rapamycin treatment led to lower regeneration. This suggests a new role for CsA in the regulation of nerve regeneration.

Dr. Butler is now focusing efforts on identifying compounds that can increase the rate of nerve regeneration without compromising the immune system. High throughput screening of human stem cell-derived motor neurons identified three compounds that led to an 80% increase in axon length. These drugs will be candidates for future investigations.

Improving Ischemia Reperfusion Injury in Vascularized Composite Tissue Allotransplantation via Histone Deacetylase Modulation

Matthew H. Levine, MD, University of Pennsylvania

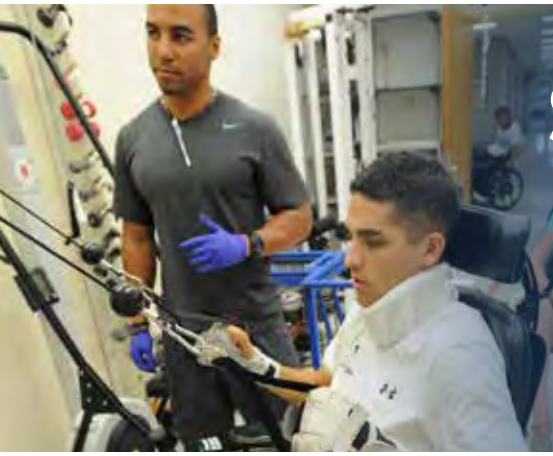
Widespread use of VCA as a treatment option for traumatic injuries has been limited, due in part to difficulty in finding matching donors. Unlike solid organ transplants, the external nature of the VCA graft requires careful matching of size, gender, skin tone, and age, in addition to blood type and immunological compatibility. Further limiting the potential donor pool is the ischemia reperfusion injury that develops as a result of cold preservation and lack of blood flow to the graft following procurement, which further reduces the potential donor pool to those within geographic vicinity of the recipient.

Dr. Matthew Levine and his team received a FY15 Idea Discovery Award to translate the success seen using histone deacetylase (HDAC) inhibitors to improve cold storage tolerance in mouse models of kidney transplants to VCA. Using a tourniquet-based warm model of ischemia injury, mice were treated with HDAC inhibitors prior to limb ischemia, and muscle injury was assessed by histology. Treatment with the HDAC-6 specific inhibitor, Tubastatin A (TubA), had the greatest protective effect against ischemia injury resulting in significantly less tissue injury compared to controls and other HDAC inhibitors. Dr. Levine's team is currently evaluating TubA in a cold ischemia model of mouse hind limb transplantation to confirm these findings. Strategies to improve graft preservation will be instrumental to increasing the accessibility of VCA to patients with significant traumatic injuries and lessening wait times for donor/recipient matches.

Christopher Marsh – From Military Medic to Wounded Warrior

Christopher Marsh had been serving as a Fleet Marine Force Navy Corpsman stationed with the Marines for his second combat tour in Afghanistan when he was shot in the left forearm during a Taliban ambush, shattering his ulna and denying his team their medical support. He wasn't able to see his wound fully to understand the extent of his injury until he arrived in San Diego 2 weeks later. It was then that he learned his injury was worse than he had originally perceived and doctors cautioned he could lose his arm. He underwent a total of 8 different surgeries to save his arm, 12 laser surgeries to minimize scarring, and extensive rehabilitation to regain hand function. He worked hard to meet the function milestones set for his recovery and with only a couple weeks to spare before his appointment with the Medical Evaluation Board, he was declared fit for duty and went on to reenlist and deploy again in a humanitarian effort.

Chris served on his first RTRP review panel in 2016, offering a unique perspective to the panels on which he serves by combining his training as a military medical provider and a Wounded Warrior. In Chris' words: "All kinds of medical developments have come out of the last 15 years of conflict, and that's driven by these types of programs that are designed to ensure that we're doing right by our Warriors and taking care of them when they come home. We're taking care of those who sacrificed for our country, and I'm very proud to be a part of it."



Spinal Cord Injury Research Program

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

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

Program History

The 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 $247.85M in congressional appropriations between FY09 and FY18, the SCIRP is now a leading funder of spinal cord injury (SCI) research in the United States. The SCIRP supports the translation of more effective strategies across the continuum of care from management of the acute injury through rehabilitation and restoration.

Program Portfolio

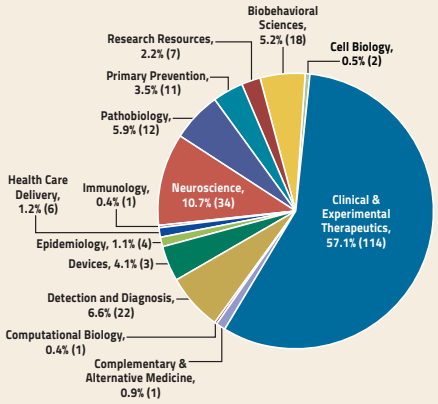
The SCIRP has funded 235 awards through FY18 across basic research, pathology detection, and diagnosis of SCI, with the largest investment in clinical and experimental therapeutics—reflecting the program's emphasis on translational and clinical research.

"The perspective of different stakeholders in the SCI community brings a richness to the program. I love the fact that there are people with lived experience as well as clinicians on the panel to give the "boots on the ground" insight."

Jennifer French, SCIRP Programmatic Panel Member, Consumer Reviewer

"There's a lot of positive energy and a great deal of commitment within the scientific community to find a cure for SCI."

James Howard (Army Captain, Retired), SCIRP Peer Review, Consumer Reviewer



FY09-FY18 SCIRP Portfolio Investment by SCS Code

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 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
- Bladder dysfunction, bowel dysfunction, and neuropathic pain
- Psychosocial issues relevant to SCI in individuals with SCI and their caregivers
- Rehabilitation and regeneration—maximizing the function of the residual neural circuitry, including harnessing neuroplasticity and recovery to improve function after SCI

Moving from Discovery to Clinical Implementation

Over the last 2 years SCIRP has funded eight Translational Research Awards. These studies are developing biomarkers for diagnosis of the initial injury, strategies to improve protection and regeneration of the injured spinal cord, and stem cell, drug, and device interventions to improve bladder and bowel function after injury.

INTRAVESICLE LACTOBACILLUS TO REDUCE URINARY SYMPTOMS AFTER SPINAL CORD INJURY
Suzanne Groah, MD, MedStar Health Research Institute

TARGETING IMPROVEMENTS IN BOWEL FUNCTION AND QUALITY OF LIFE USING EPIDURAL STIMULATION AND TRAINING AFTER SEVERE SPINAL CORD INJURY
April Herrity, DC, PhD, University of Louisville Research Foundation, Inc.

ASSESSMENT OF SELECTIVE INHIBITORS OF NUCLEAR EXPORT (SINE) FOLLOWING SPINAL CORD INJURY
Caitlin Hill, PhD, Neural Stem Cell Institute, Regenerative Research Foundation

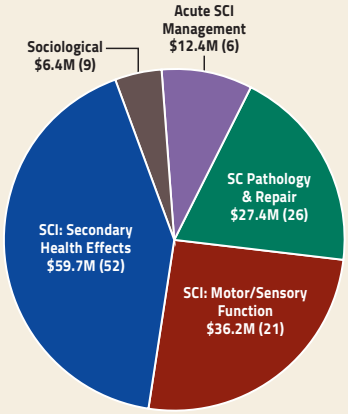
ULTRASOUND-BASED BIOMARKER TO IDENTIFY TISSUE AT RISK FOR SECONDARY INJURY AFTER TRAUMATIC SPINAL CORD INJURY
Christoph Hofstetter, MD, PhD, University of Washington

NEOSTIGMINE AND GLYCOPYRROLATE BY IONTOPHORESIS TO INDUCE BOWEL EVACUATION
Mark Korsten, MD, VA Medical Center, Bronx, NY

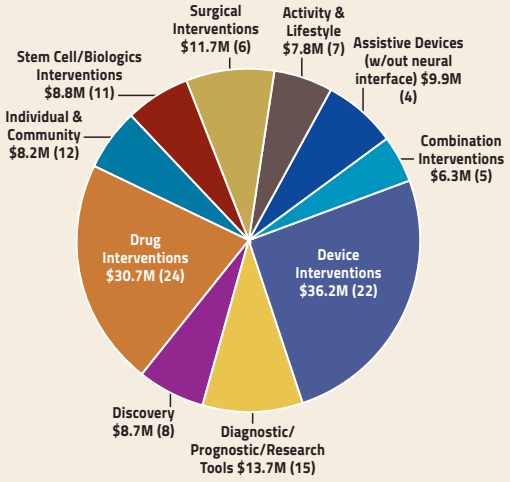
AMBULATORY BLADDER MONITORING AFTER SPINAL CORD INJURY
Brian Kwon, MD, PhD, University of British Columbia

AN INNOVATIVE REPAIR STRATEGY TO TARGET INHIBITORY GLIA SCARS AFTER SPINAL CORD INJURY
Yu-Shang Lee, PhD, Cleveland Clinic Foundation

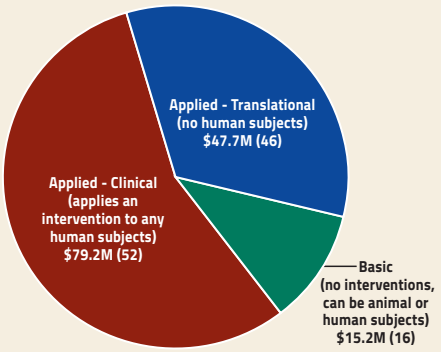
EFFECTS OF HUMAN NEURAL STEM CELL GRAFTS ON AUTONOMIC AND CARDIOREGULATORY SYSTEMS AFTER SCI IN NON-HUMAN PRIMATES
Mark Tuszynski, MD, PhD, University of California, San Diego



System/Problem



Approach/Intervention



Readiness/Stage

Spinal cord injuries are serious and complex neurotraumatic wounds that require multiple approaches to address problems of acute management, rehabilitation, and care throughout the lifetime of the individual. The figures above show the current SCIRP investment (active awards as of September 30, 2019, funding shown by dollars in millions and number of awards) addressing problems from management of acute SCI through spinal cord pathology and repair, and on to treatment of secondary health effects—including neuropathic pain, pressure ulcers and bladder and bowel dysfunction. Approaches supported include discovery of important biological mechanisms in SCI, as well as development of interventions using drug, device, stem cell, and surgical approaches. Although the SCIRP does support basic research, the program focuses on translation and clinical studies to meet the mission of developing and translating effective strategies to improve the health and well-being of individuals with SCI.

Tick-Borne Disease Research Program

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

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

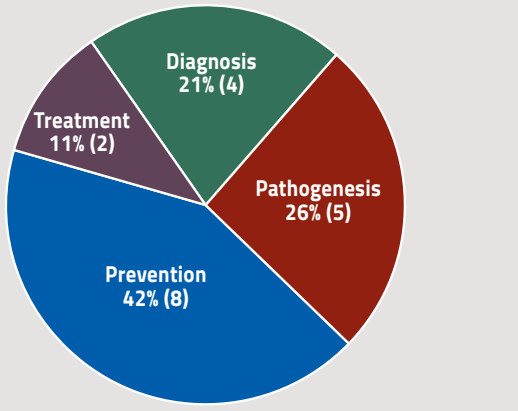
Program History

The Tick-Borne Disease Research Program (TBDRP) was established in FY16, when the efforts of Lyme disease advocates led to a congressional appropriation of $5M. The TBDRP has received funding at a rate of $5M annually, totaling $20M for the period FY16-FY19. 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).

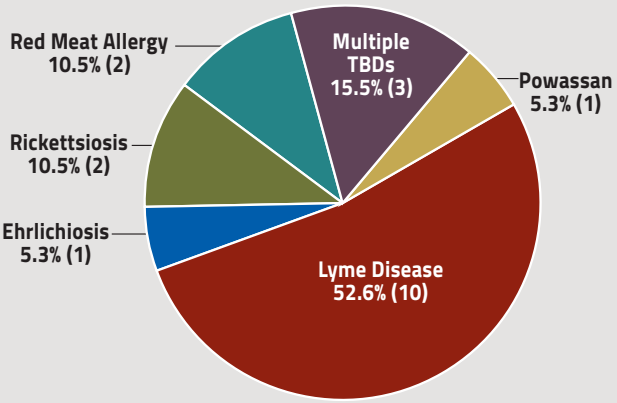
Overarching Challenges

There are now at least 18 known infectious tick-borne pathogens, with 20 conditions and 13 illnesses resulting from tick bites.[1] As tick populations grow and expand geographically, annual cases of Lyme disease and other TBDs, including spotted fever rickettsiosis, anaplasmosis, and ehrlichiosis, continue to increase with tens of thousands of new cases annually and more likely going undiagnosed.

Continued research efforts are critical in order to elucidate mechanisms of TBD pathogenesis, including host-pathogen interactions and the human immune response to these pathogens. There is a need for strategies to prevent tick bites by controlling the natural cycle of disease transmission and by developing methods to protect people from tick bites. Once an individual is bitten, it is vital that diagnostic tools are available for the direct detection of the tick-borne pathogen or detection of the host biomolecular signature. This will allow treatment to be tailored and initiated rapidly in patient populations suffering from acute and persistent symptoms due to Lyme disease or other tick-borne illnesses.



FY16-FY18 TBDRP Portfolio by Focus Area/SCS Code[2]



FY16-FY18 TBDRP Portfolio by Disease Classification[2]

[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] Percentage of total TBDRP funded studies, (number of awards)

Program Goals and Strategy

The TBDRP has offered award mechanisms focused on career development, new ideas and discovery, and established research in order to address research gaps in the Focus Areas of diagnosis, pathogenesis, prevention, and treatment of Lyme disease and other TBDs that increasingly impact civilian and military populations. As the TBD field works to understand the mechanisms of tick-borne pathogen infection, persistence, immunomodulation, and pathology, the TBDRP aims to support researchers in building on their findings to pursue further optimization and preclinical development, as well as eventual validation and translation of these advancements. The outcome of addressing fundamental questions in TBD research is a more thorough understanding of complicated TBD processes, including the implications of co-infections, molecular effects on the host response, and mechanisms of Lyme disease persistence, to name a few. Together, the products of these studies will positively impact military Service members and the American public by improving the tools used for TBD diagnosis and treatment.

Consumer Perspective

Holiday and Olivia Goodreau, TBDRP Consumer Peer Reviewer:

Second-grader Olivia Goodreau began experiencing body aches, brain fog, headaches, and other persistent symptoms. After 18 months, visiting over 55 doctors, Olivia was finally diagnosed with Lyme disease in 2013. Together, Olivia and her mother, Holiday, founded the LivLyme Foundation,[3] which promotes research and patient support for those with Lyme disease. They also developed a free mobile application called TickTracker[4] that allows users to track and report ticks in real-time using their geographical location.

Holly Ahern, TBDRP Consumer Peer Reviewer:

"The inclusion of Consumer Reviewers in the CDMRP grant review process is an important way to connect the patient narrative to research projects that will advance the science of their disease. As both a scientist and mom of a Lyme disease patient, it was an empowering experience to know that the patient perspective is taken into consideration as decisions on which research projects to fund are being made."

Funded Investigator Perspective

Ying Zhang, MD, PhD, Johns Hopkins, Bloomberg School of Public Health

"There is currently no FDA-approved treatment for persistent Lyme disease despite the projection that it will affect 2 million people by 2020. Completion of our TBDRP-funded project will help to develop more effective treatments for the persistent Lyme disease."

Charles Chiu, MD, PhD, University of California, San Francisco

"The clinical diagnosis of Lyme disease and other tick-borne illnesses is challenging. With funding from the TBDRP, we are leveraging next-generation sequencing technology for the development of accurate diagnostic tests that will drive clinical trials and effective therapies."

Yoonseong Park, PhD, Kansas State University

"Red meat allergy (RMA) is an emerging TBD in the US and worldwide, known to be caused by Lone Star tick bites in Southwestern states. Our TBDRP award focuses on elucidating the molecular nature of the allergen in the tick salivary gland using a mutant mouse model. Results from this study will uncover the biology and phenology of the specific ticks that cause RMA (e.g., stages, gender, and prior host) and establish guidelines for the prevention of RMA."

John S. Dumler, MD, Uniformed Services University

"With our TBDRP-funded award, we expect to identify drugs that allow us to simultaneously examine mechanisms of and abrogation of vascular permeability, as well as potential compounds to reduce severity, morbidity, and mortality for tick-borne rickettsial diseases. Should these studies prove successful, these drugs could be used as adjunct therapies to prevent the most dangerous complications and sequelae of TBDs."

[3] https://livlymefoundation.org/

[4] https://ticktracker.com/

Tuberous Sclerosis Complex Research Program

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 insight to clinical application, by supporting new ideas and investigators for the benefit of Service members, their beneficiaries, and the American public

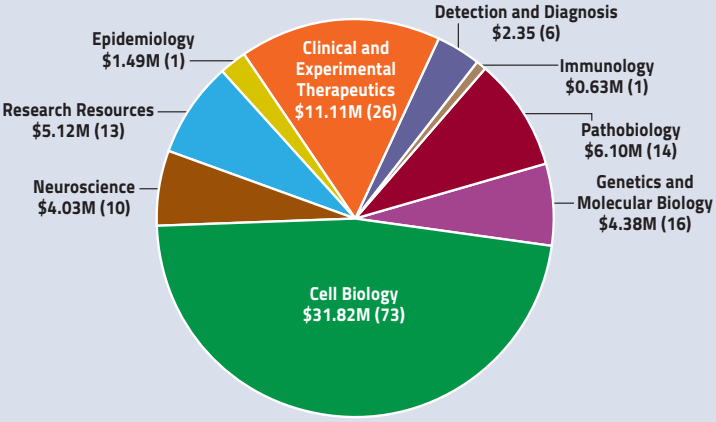
Program History

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. The incidence and severity of the various aspects of TSC vary widely between individuals–even between identical twins. TSC can be inherited as an autosomal dominant trait or can be the result of a spontaneous genetic change on TSC1 (hamartin) or TSC2 (tuberin) gene. It is estimated that TSC affects approximately 50,000 individuals in the United States, and 1 to 2 million individuals worldwide. Many cases may remain undiagnosed for years or decades due to the relative obscurity. The Tuberous Sclerosis Complex Research Program (TSCRP) was first funded in FY02, when the efforts of TSC advocates led to a congressional appropriation of $1M. Since then, a total of $83M has been appropriated to the program, including $6M in FY19.

The TSCRP has funded 160 awards through FY18 to support high-impact, innovative research; foster the development of research resources and tools; promote the translation of new research findings to patient care; and advance the knowledge of TSC and its clinical manifestations.

"For all the TSC families that take Washington DC by storm every year to advocate for funding for this awesome research program, please know your hard work is making a difference. While it's never fast enough in the eyes of those affected, the science is advancing rapidly. Guided by a new *Strategic Plan* developed in 2018, TSCRP is an extraordinarily effective program that achieves results! I am honored to be a participant in this process of finding a cure, and I always say it's the most important thing I can do to help my son, Bao, now and into the future."

Ron Heffron, P.E., Tuberous Sclerosis Alliance
TSCRP Programmatic Panel Member



FY02-FY18 TSCRP Portfolio Investment by SCS Code (Number of Awards)

Gene Therapy, a New Approach to Treating TSC

Xandra O. Breakefield, PhD
Massachusetts General Hospital

Rapamycin analogues, currently used to treat TSC, are effective but have a number of limitations including expense, the need for continual treatment, reduced access to the brain, and potential interference with brain development in young children. Gene therapy is an attractive alternative to conventional TSC treatments in that it can be given with only a single application, has limited side effects, and has been proven effective in several genetic diseases. With a TSCRP Exploration – Hypothesis Development Award, Dr. Breakefield and her team are investigating gene therapy as a potential therapeutic approach for TSC. They have developed a preclinical mouse model of TSC in which the TSC1 or TSC2 gene are missing in some brain cells starting at the time of birth. These mouse models led to early death due to accumulation of fluid in the brain (hydrocephalus) and abnormal electrical activity (epilepsy). By introducing the missing gene into the bloodstream via an adeno-associated virus vector, a carrier used to deliver missing genes to recipient cells, prior to death, Dr. Breakefield was able to normalize brain structures and extend the lifespan to almost normal length in mouse models of both TSC1 and TSC2. Currently, Dr. Breakefield is optimizing a vector for whole body systemic delivery, as well as investigating the biological impact of gene replacement. With a patent currently submitted for her work, Dr. Breakefield is looking to partner with a biotechnology company in hopes of developing a clinical grade vector that can be evaluated in clinical trials of TSC.

Repurposing FDA-Approved Drugs to Treat TSC

Benjamin Housden, PhD
University of Exeter, United Kingdom

Current treatments for TSC only block or slow down tumor growth and require continual administration to prevent tumor reoccurrence. As a member of Dr. Norbert Perrimon's lab at Harvard University, supported by a TSCRP Idea Development Award, Dr. Benjamin Housden used Drosophila (fruit fly) cells to develop a novel screening approach capable of identifying genes susceptible to therapeutic treatment to specifically kill cells with TSC1 and TSC2 mutations. With funding from a TSCRP Exploration – Hypothesis Development Award, Dr. Housden is expanding upon this previous work by further developing the screening approach and testing candidate drugs, identified in Drosophila cell screens, in human cells. Dr. Housden is looking to identify genes that, when targeted in conjunction with a TSC mutation, cause cell death (synthetic sick or lethal [SS/L] interactions). In an effort to minimize the delay in translating successful drugs from benchtop to bedside Dr. Housden is focusing on identifying existing FDA-approved drugs that can be repurposed for the treatment of TSC, either alone or in combination. Based on his preliminary high-throughput Drosophila screens, four drugs have shown promise as viable candidates to treat TSC. Further studies with patient-derived TSC cells indicate that two of these candidates have potential to translate into successful treatment, and that using a combination of FDA-approved drugs yields more effective treatment of TSC cells than any single drug alone.

"Participating on the peer review panel required hard work, dedication, and commitment, and it was truly amazing. One of the most rewarding parts of this experience was the panel itself: the respectful and thoughtful conversation and the wealth of knowledge, both scientific and personal, all coming together for a unified purpose. The scientific reviewers were incredibly grateful that we shared our experiences with them. Their commitment to the research motivates the TSC community to go out and advocate for this funding, and our passion and experiences living with TSC motivate the researchers to continue to do their work, with the joint goal of better understanding the pathogenesis and manifestations of TSC in order to improve the lives of individuals with TSC."

Tara Zimmerman-Tuttle, Tuberous Sclerosis Alliance, TSCRP Consumer Peer Reviewer

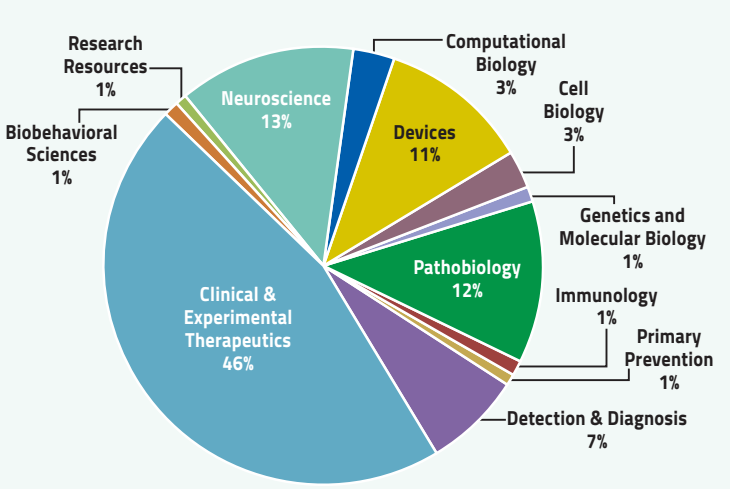
Vision Research Program

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

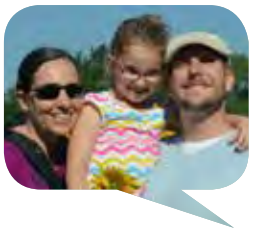
Mission: To identify and address clinical needs through directed medical research to improve the health and readiness of military personnel affected by eye injuries and vision dysfunction

Program History

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, TBI, which affects ~380,000 Service members according to statistics from the Defense and Veterans Brain Injury Center, 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 had visual dysfunction. The DOD Vision Research Program (VRP) was established by Congress in FY09 to fund impactful military-relevant vision research that has the potential to significantly improve the health care and well-being of Service members, Veterans, their family members and caregivers, and the American public. The VRP received $84.95M in congressional appropriations in FY09-FY18. The FY19 VRP appropriation is $20M.



FY09-FY18 VRP Portfolio Investment by SCS Code



"There simply is no other funding mechanism in existence that focuses solely on military-related eye traumas and visual impairments. It is for this reason I proudly serve as a representative of the Blinded Veterans Association on the VRP, hoping tomorrow's warfighters may be prevented from living life with a visual impairment."

CPT (Ret) Timothy Hornik, Blind Veterans Association, VRP Consumer Peer Reviewer

New Mechanism: Focused Translational Team Science Award (FTTSA)

In FY18, the VRP initiated the FTTSA mechanism to support highly collaborative and translational team initiatives that will fundamentally advance understanding and treatment of eye injury and/or visual dysfunction resulting from a military-relevant traumatic event. Through the FTTSA, the VRP challenges investigators to bring together 3-5 distinct yet collaborative research projects to synergistically address an overarching challenge or question. The following FTTSA application was selected for funding by the FY18 VRP:

Development of Diagnostic, Prognostic, and Therapeutic Tools for Battlefield Optic Nerve Trauma

Leonard A. Levin, MD, PhD (pictured), McGill University; Adriana Di Polo, PhD, University of Montreal; H. Uri Saragovi, PhD, McGill University; Jeanine Mendola, PhD. McGill University; and Amir Shmuel, PhD, McGill University

A collaborative effort led by Dr. Leonard Levin is addressing the issue of traumatic optic neuropathy (TON), which is a major cause of permanent blindness on the battlefield. In Operations Iraqi Freedom and Enduring Freedom, TON was seen in 20% of Soldiers with vision loss and 27% of those with severe vision loss. The collaboration involves three interactive projects led by five primary scientists with complementary and synergistic specialties. Dr. Levin and Dr. Adriana Di Polo lead the first project, which focuses on translational models and testing of new therapeutic agents for TON. Dr. Uri Saragovi, a leading expert on pharmacology, leads Project 2 to develop and optimize new pharmacological compounds that will be evaluated in Project 1. The third project, led by functional neuroimaging experts Dr. Jeanine Mendola and Dr. Amir Shmuel, aims to develop non-invasive brain imaging for the diagnosis, treatment and prognosis of TON. The new diagnostic tools and protocols will be incorporated into the animal studies in Project 1. If successful, this multidisciplinary collaboration will generate a complete, first-in-kind toolbox of novel diagnostic, prognostic, and therapeutic strategies for TON that will serve as a springboard to design pilot clinical trials.

VRP Research Outcomes

Modulating Macrophages to Prevent Corneal Neovascularization

Ali Djalilian, MD, University of Illinois

Severe injuries and infections of the cornea can lead to corneal neovascularization (CNV), a pathologic condition where blood vessel grow into the cornea, causing significant scarring and loss of vision. CNV is particularly common in the setting of severe chemical and thermal burns to the cornea, both highly relevant to combat related eye injuries. Although there are several treatment options, the visual outcomes are not optimal given the extensive tissue destruction. With support from a FY14 Translational Research Award, Dr. Djalilian performed research focusing on a therapeutic treatment using mesenchymal stromal cells (MSCs). They showed that MSCs can promote corneal tissue repair and prevent CNV in experimental models of severe corneal injury. Mechanistically, they showed for the first time that corneal-derived MSCs not only secrete factors that inhibit CNV, but also modulate macrophages to increase the secretion of anti-inflammatory and anti-angiogenic factors. These results were published initially in 2017 followed by a 2018 publication in *Stem Cells*, where Dr. Djalilian concluded that tissue-specific MSCs can be used for targeted immunomodulatory and anti-angiogenic cell-based therapies.[1] This could help prevent vision loss and restore quality of life for Service members and the public suffering from severe corneal injuries and wound healing disorders. Dr. Djalilian has received an FY17 Clinical Trial Award to continue his work to make this novel therapy available to patients.

[1] Eslani M, Putra I, Shen X, et al. 2018. Cornea-derived mesenchymal stromal cells therapeutically modulate macrophage immunophenotype and angiogenic function. *Stem Cells* 36(5):775-784.

Shedding New Light on Retinal Ganglion Cell Injury with Matrix-Bound Nanovesicles

Stephen Badylak, DVM, PhD, MD, University of Pittsburgh

Retinal ganglion cells (RGCs) relay visual information from the retina to the brain. Ischemia, the restriction of blood supply to tissues, may be caused by a severe increase in intraocular pressure (IOP), with the subsequent effect of RGC degeneration and loss of visual function. Research by Drs. Badylak and Steketee, funded in part by a FY14 Translational Research Award, has demonstrated that matrix-bound nanovesicles (MBV) can help prevent this degeneration and preserve visual function in rats.[1] Dr. Badylak's work has shed new light on the effects of MBV on RGC integrity, connectivity, and visual function. MBV have the potential to be utilized as a therapy for patients suffering from IOP-related eye injuries.

[1] van der Merwe Y, Faust AE, Sakalli ET, et al. 2019. Matrix-bound nanovesicles prevent ischemia-induced retinal ganglion cell axon degeneration and death and preserve visual function. *Scientific Reports* 9(1):3482.

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.

Additional Supported DOD Programs/Projects

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 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 PAs, solicitation and review of applications, full life-cycle management of awards, and program evaluation and planning.

Program and Portfolio Areas

From FY10-FY18, CDMRP helped to manage approximately $815.7M invested in DMDRP awards ranging from basic, translational, and clinical research efforts (including CRII). 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://mrmc.amedd.army.mil/index.cfm?pageid=medical_r_and_d.msis.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*

Affiliated Research Programs

- JWMRP
- Psychological Health and Traumatic Brain Injury Research Program (PH/TBIRP)

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

- Investigational New Drug Enabling Development of CF-296, a Lysin for the Treatment of Invasive Staphylococcus Aureus Infections – *Raymond Schuch at ContraFect Corporation*
- Development of SPR206, a Direct Acting Polymyxin Antibiotic with Reduced Nephrotoxicity, to Treat Multidrug-Resistant Gram-Negative Bacterial Pathogens – *Michael Pucci at Spero Therapeutics (award still under negotiation)*
- Biomimetic Adhesive with Antimicrobial Properties and the Ability to Promote Wound Healing - *Bruce Lee at Michigan Technological University*

Affiliated Research Programs

- JWMRP
- PRMRP
- TBDRP

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

- Warfighter Recovery Nutrition: Optimizing Protein Quantity, Quality, and Combat Ration Delivery Systems – *Amy Ferrando at University of Arkansas for Medical Sciences*
- 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*

Affiliated Research Programs

- ASADRP
- GWIRP
- JWMRP
- PRMRP
- PH/TBIRP

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

- Genomics-, Microbiomics-, and Bioenergetics-Based Personalized Treatment for Trauma Patients at Risk for Sepsis – *Catriona Miller at 711th Human Performance Wing United States Air Force*
- Wireless Microsensor to Continuously Monitor Compartment Pressure in Trauma Victim – *Edward Harvey at McGill University Health Centre Research Institute*
- Theranostic Cellular Backpacks for Precision Imaging and Treatment of Traumatic Brain Injury Sites – *Samir Mitragotri at President and Fellows of Harvard College*

Affiliated Research Programs

- ERP
- JWMRP
- MBRP
- PRMRP
- PRORP
- PH/TBIRP
- SCIRP
- Trauma Clinical Research Program

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

- Further Development of dmPGE2 as an Effective Radioprotectant and Radiomitigator for H-ARS and DEARE in Fulfillment of the Requirement for Product Development Under the Animal Rule – *Christie Orschell at Indiana University of Indianapolis*

Affiliated Research Programs

- JWMRP
- PRCRP
- PRMRP

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)

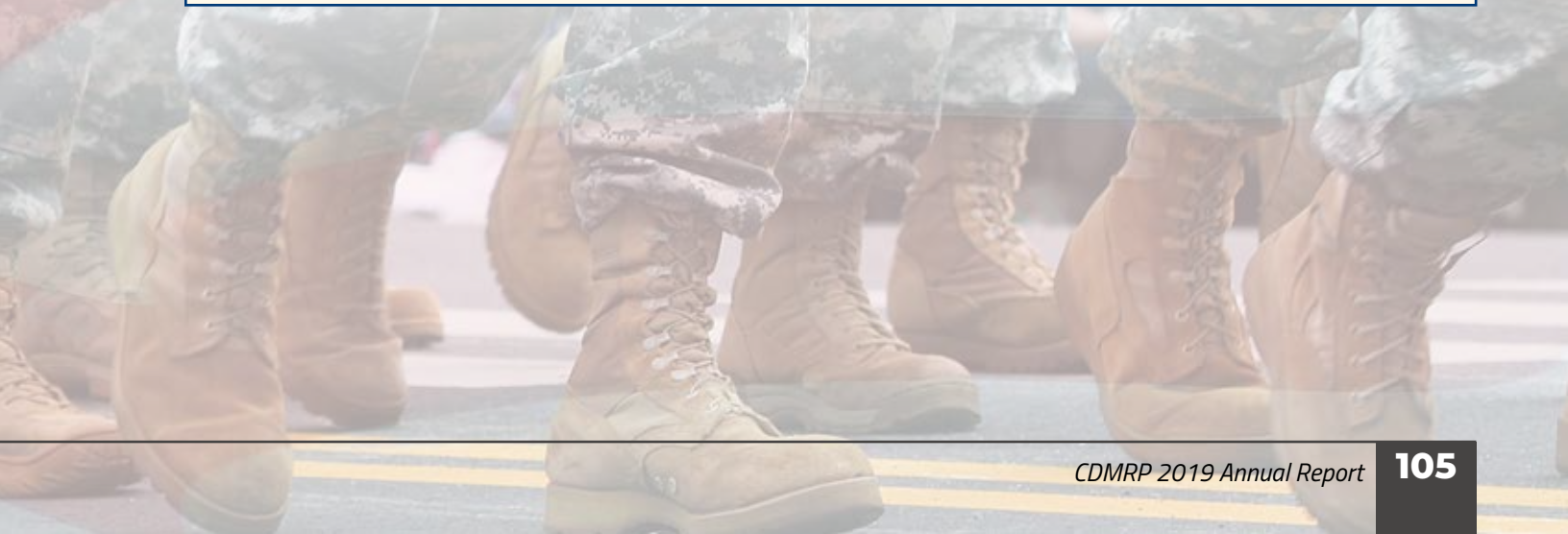
CRMRP's mission is to implement long-term strategies to develop knowledge and materiel products to reconstruct, rehabilitate, and provide definitive care for injured Service members. The ultimate goal is to return the Service member to duty and restore their quality of life. Additional information about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

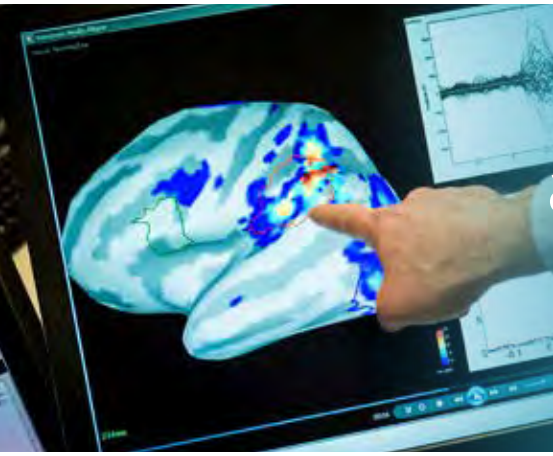
Recent CRMRP DHP Research

- 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*

Affiliated Research Programs

- HRRP
- JWMRP
- OPORP
- PRMRP
- PRORP
- PH/TBIRP
- RTRP
- SCIRP
- 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 FY18, CDMRP has managed 565 Psychological Health and Traumatic Brain Injury Research Program (PH/TBIRP) awards, totaling over $1037.4M 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 FY17, 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 PAs, 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

- Mindfulness-Based Attention Training to Bolster Small Team Performance – *Amishi Jha at the University of Miami at Coral Gables*
- Peer-to-Peer Programs for Military Suicide Prevention – *Craig Bryan at the University of Utah*
- Patterns of Alcohol Use and Suicide-Related Thoughts Among Recently-Discharged Veterans: Risk Factors Associated with the Military-to-Veteran Transition – *Samuel Bacharach at Cornell University at Ithaca*

CCCRP

- Biomarkers for Detection and Treatment of Traumatic Brain Injury – *Harshini Mukundan at Los Alamos National Laboratory*
- A New "Medical Record for the Brain" Enabling Precision Management of TBI – *Richard Moberg at Moberg Research Incorporated*
- Precision Intracranial Bleed Triage and Monitoring – *Seth Wilk at Neural Analytics*

CRMRP

- Implementation of a Brief Cognitive Rehabilitation Intervention to Enhance Efficiency of Service Delivery for Service Members and Veterans with mTBI: core-SCORE – *Laurie King at South Texas Veterans Health Care System*
- Objective Dual-Task Turning Measures for Return-to-Duty Assessment – *Blessen Eapen at Oregon Health and Science University*

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

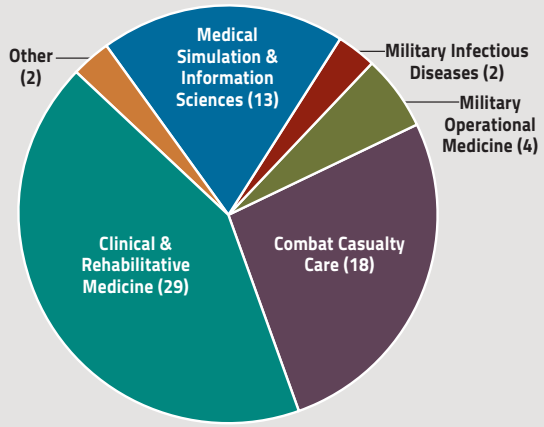
Mission: To address military medicine needs through topic development and management oversight of R&D projects, in support of broader SBIR/ STTR goals

Program History

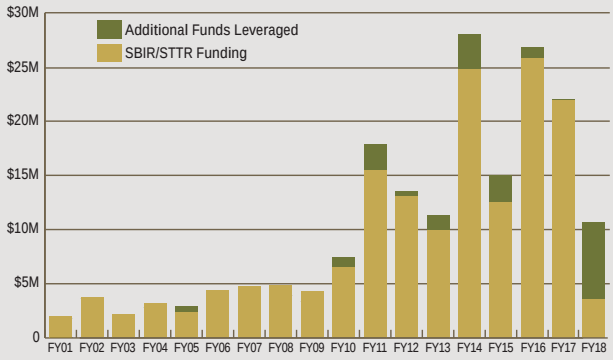
Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) are highly competitive programs that encourage US small businesses to engage in R&D with the incentive to profit from the product's commercialization. The programs are organized in three phases: Phase I establishes 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. Although CDMRP does not manage these programs, CDMRP supports four distinct SBIR/ STTR programs hosted by USAMRDC: Army SBIR, Army STTR, DHA SBIR, and DHA STTR. In addition to providing project management oversight, CDMRP personnel collaborate with JPCs and PADs to develop topics and review proposals on behalf of the programs. CDMRP supports the projects through all phases of development.

Approved DOD SBIR and STTR topics are announced online at http://www.acq.osd.mil/osbp/sbir/solicitations/index.shtml.



FY11-FY19 SBIR/STTR Topics by Program Area



Total SBIR/STTR Funds Managed by CDMRP

Projects Advancing Through the Phases

Topic Solicitation Year	Topics Managed by CDMRP	Phase I Awards	Phase II Awards	Additional Funding*
2011	14	50	18	5
2012	9	30	9	4
2013	10	17	15	1
2014	2	6	4	2
2015	9	22	13	1
2016	7	19	12	2
2017	8	25	15	0
2018	3	6	1	0
Totals	**62**	**175**	**87**	**12**

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

Cognitive/Motor Therapy Application Using Console-Based Videogame Platform

Recovery from injuries causing cognitive and physical impairments requires many hours of therapy in the clinic with continued practice at home. The therapy can be tiresome and demanding and is rarely fun. In addition, patients lack tools to self-evaluate their progress. Finally, clinicians lack the ability to track their patient's home program or update the program based on their patient's progress. Blue Marble Health, with the support of Phase I, II, and IIB SBIR funding is changing all of that. They have developed the Blue Marble Health Platform that contains self-assessments, games, a health diary, educational modules, and goal setting tools to empower patients to keep track of their health, their recovery from injury, and their management of chronic conditions. Furthermore, clinicians can track their patient's progress, create home programs, and create population health status reports, all from the Blue Marble Health web app. The Blue Marble Health platform has been validated and is currently being commercialized. Research supporting the Blue Marble Platform was funded by both DOD (DHA) and NIH SBIR grants and contracts. Concurrent validity studies of cognitive domains demonstrated correlations ranging from .196-.569 when compared with gold standard assessments. Non-inferiority was demonstrated comparing the Blue Marble cognitive intervention and assessments with commercial web-based cognitive interventions. The findings suggest that both groups demonstrated improved cognitive function across four domains (Attention, Executive Function, Memory, and Visual Perceptual Processing). Executive function domain demonstrated the greatest amount of improvement.

Screenshot of one of the cognitive tests that measures associative memory.

Utilizing the Healing Properties of Silk to Treat Ocular Trauma

Ocular injuries sustained by the United States military forces in combat have traditionally comprised over 17% of total war injuries. Silk Technologies, Ltd. (SilkTech) has received several Army SBIR awards to develop an eye drop formulation with anti-inflammatory and regenerative properties to accelerate the wound healing process for corneal abrasions. The basis for this formulation is silk-derived protein (SDP), which is extracted from the cocoons of *Bombyx mori* silk worms and contains a mixture of many different sized proteins with varying properties. During Phase I, SDP was separated by size-exclusion chromatography and the resulting fractions were analyzed. SDP-4 was identified as the fraction with greatest anti-inflammatory efficacy, while also stimulating corneal epithelial cell proliferation and migration (i.e., wound closure) to the greatest extent, by over 25%. During Phase II, SilkTech optimized the formulation and evaluated the toxicity profile and long-term stability of the SDP-4 eye drop formulation in an in vivo rabbit model. Under good laboratory practice guidelines, the rabbits tolerated a four times daily dose of SDP-4 over a three month period with no adverse effects. An Investigational New Drug submission to the FDA occurred during the first quarter of 2019. SilkTech is currently working under a Phase II Enhancement award to validate the SDP-4 manufacturing processes under good manufacturing practice (GMP) controls, as well as develop and validate the GMP-qualified test methods for clinical grade SDP-4 eye drop. A first in human clinical trial began in April 2019 under other funding with a completion date anticipated in late 2019.

Trauma Clinical Research Program

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

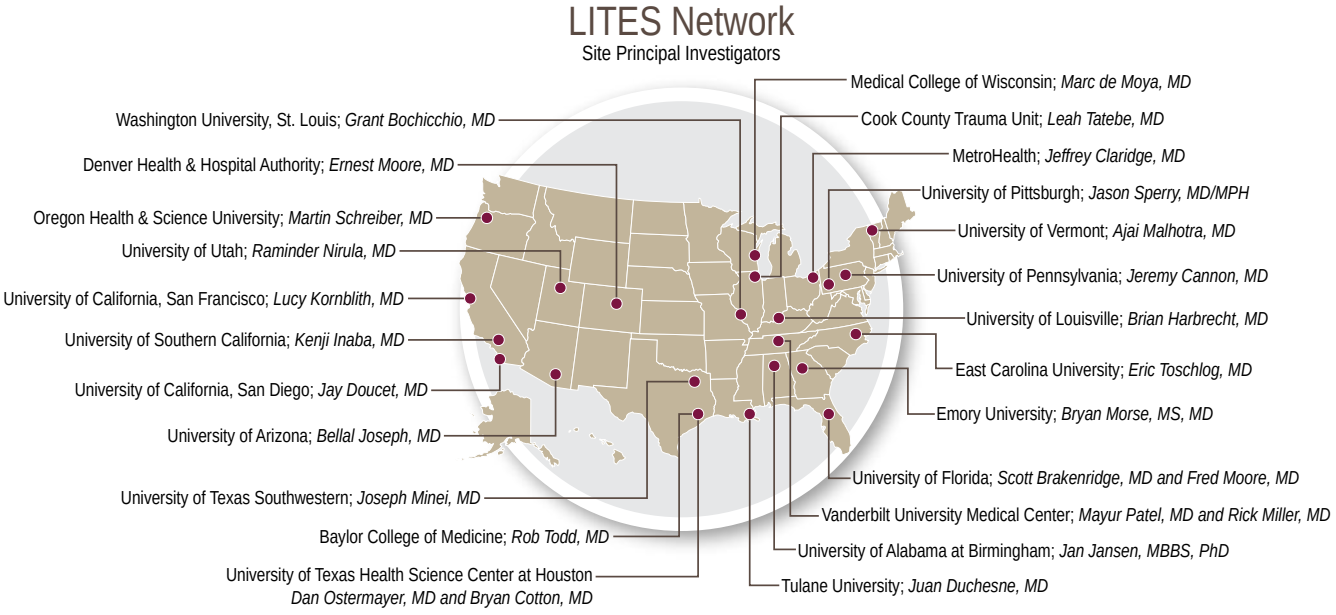
Mission: To address the military relevant priorities and gaps in trauma care and facilitate the transition of lessons learned into best practice guidance and products

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.

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 2019, there are 22 LITES Network Sites and additional information is located at www.litesnetwork.org.



LITES Research Task Orders

TASK ORDER #01

The aims of Task Order #01 are: (a) to characterize the epidemiology of moderate and severe physical injury in the US and the LITES Network and (b) 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 and update existing trauma standards of care for both military and civilian populations. This inaugural Task Order is a 5-year prospective multicenter observational cohort study. The target required for clinical significance is 50,000 subjects. As of May 2019, approximately 29,853 subjects have been enrolled across eight participating trauma centers. The participating trauma centers are University of Pittsburgh, University of Texas Health Science Center-Houston, University of Arizona-Tucson, Baylor College of Medicine-Houston, Oregon Health and Science University-Portland, Vanderbilt University Medical Center, University of Louisville, and Denver Health and Hospital.

TASK ORDER #02

Task Order #02 is a study to characterize acute resuscitation using two standards of care, whole blood and component therapy, and to determine the effects of resuscitation practices, including blood use and permissive hypotension, on secondary brain injury. Despite its historical and more recent use on the battlefield and a limited number of US trauma centers, little is known regarding the benefits of whole blood relative to the current practice of "ratio-based blood component therapy" in the acutely bleeding patient, and even less is known regarding its effects in patients with TBI. The aims of Task Order #02 are: (a) to evaluate patient-centered outcomes associated with early whole blood resuscitation practices as compared to component resuscitation in poly-trauma patients with hemorrhagic shock and to further characterize outcome benefits in those with TBI and (b) to characterize blood pressure and resuscitation endpoints during the acute resuscitation phase of care and the associated/attributable outcomes for TBI in patients with hemorrhagic shock. Task Order#02 data will be collected for an initial study period of 4 years, and the projected subject enrollment is 892. As of May 2019, 195 subjects have been enrolled across six participating trauma centers. The participating trauma centers are University of Pittsburgh, University of Texas Health Science Center-Houston, Oregon Health and Science University-Portland, University of Pennsylvania-Philadelphia, and University of Texas Southwestern-Parkland. Task Order #02 is open for enrollment and actively enrolling patients.

TASK ORDER #05

Pre-hospital trauma airway management is a low frequency high consequence event for both military and civilian providers. Airway management failures account for 8%-15% of combat deaths deemed to be potentially preventable. Task order #05 is a 5-year (4-year enrollment) randomized, multi-center trial of pre-hospital trauma airway management, comparing 24-hour survival following placement of and endotracheal tube versus a supraglottic airway. The aims of the study are: (a) to compare the effect of initial endotracheal intubation (ETI) versus initial supraglottic airway upon 24-hour survival after traumatic injury, (b) to compare the effect of initial ETI versus initial supraglottic airway upon hospital survival after traumatic injury, and (c) to compare the effect of ETI versus initial supraglottic airway upon major adverse events after traumatic injury. The target enrollment for clinical significance is 2,040 subjects. Subjects will be recruited and enrolled from the following LITES network sites:

University of Pittsburgh, East Carolina University, Tulane University, Oregon Health and Science University-Portland, Washington University, Vanderbilt University, Tulane University, and Cook County Hospital of Chicago. Study findings will provide critical important information as to whether a simpler pre-hospital airway management method (supraglottic airway) will improve survival outcomes at a lower cost.

Appendix A: FY92-FY18

Table A-1. Overview of Appropriations, Applications Received, and Awards Made for FY92-FY18

Programs Managed by CDMRP	Fiscal Year	Appropriations Received (in millions)	Applications Received	Applications Funded[1]
Alcohol and Substance Abuse Disorders[1]	2014-2018	$20.0	12	7
Amyotrophic Lateral Sclerosis	2007, 2009-2018	$79.4	566	73
Autism	2007-2018	$81.9	1,415	160
Bone Marrow Failure	2008-2018	$35.6	496	71
Breast Cancer	1992-2018	$3,511.3	57,439	6,883
Breast Cancer Research Semipostal[2]	1999-2018	$26.0	-	52
Chronic Myelogenous Leukemia	2002-2007	$22.1	252	61
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	2011-2018	$26.4	187	32
Epilepsy	2015-2018	$30.0	146	32
Genetic Studies of Food Allergies	2009-2010	$4.4	60	9
Gulf War Illness	2006, 2008-2018	$170.0	590	189
Hearing Restoration	2017-2018	$20.0	46	14
Institutionally Based Programs[1]	1995-2010	$486.3	306	501
Joint Warfighter Medical[1]	2012-2018	$304.0	181	78
Kidney Cancer	2017-2018	$25.0	441	51
Lung Cancer	2009-2018	$127.5	3,286	251
Lupus	2017-2018	$10.0	225	25
Military Burn[1]	2014-2018	$40.0	67	37
Multiple Sclerosis	2009-2018	$51.1	765	100
Myeloproliferative Disorders Research	2004	$4.3	18	9
National Prion Research Project	2002	$42.5	136	38
Neurofibromatosis	1996-2018	$332.9	1,642	409
Orthotics and Prosthetics Outcomes	2014-2018	$50.0	240	46
Osteoporosis	1995	$5.0	105	5
Ovarian Cancer	1997-2018	$316.5	3,891	454
Parkinson's[1]	2014-2018	$80.0	340	97
Peer Reviewed Alzheimer's[1]	2014-2018	$69.0	531	112
Peer Reviewed Cancer	2009-2018	$339.8	4,679	617

Continued on next page.

Table A-1. Overview of Appropriations, Applications Received, and Awards Made for FY92-FY18 (cont.)

Programs Managed by CDMRP	Fiscal Year	Appropriations Received (in millions)	Applications Received	Applications Funded[1]
Peer Reviewed Medical	1999-2006, 2008-2018	$2,000.7	12,841	1,377
Peer Reviewed Orthopaedic	2009-2018	$368.5	1,303	273
Prostate Cancer	1997-2018	$1,720.0	18,957	3,368
Reconstructive Transplant	2015-2018	$51.0	553	88
Spinal Cord Injury	2009-2018	$247.9	1,156	236
Tick-Borne Disease	2016-2018	$15.0	138	19
Trauma Clinical Research Repository	2014	$5.0	3	1
Tuberous Sclerosis	2002-2006, 2008-2018	$77.0	741	160
Vision	2013-2018	$68.9	393	69
Miscellaneous	-	-	-	23
Additional Supported DOD Programs/Projects				
Armed Forces Institute of Regenerative Medicine II[3]	2017-2018	$23.1	-	-
Centers of Excellence	2015-2017	$17.2	-	1
Defense Medical Research and Development[4]	2010-2018	$815.7	1,833	548
Defense Medical Research and Development CSI[5] Restoral[6]	2015-2018	$172.7		106
Psychological Health/Traumatic Brain Injury	2007, 2009-2018	$1,037.4	3,552	565
Rapid Innovation Fund	2011-2015	$35.7	-	15
Small Business Innovation Research/Small Business Technology Transfer	2014-2018	$59.1	139	203
Trauma Clinical	2016-2018	$30.0	-	-
Vision Prosthesis	2015-2016	$1.2	-	3
Other Submission Processes				
MRMC - BAA[7]	-	-	524	-
Total		**$13,205.8**	**121,936**	**17,603**

[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 2 awards; 1 fully funded and 1 partially funded.
[3] Armed Forces Institute of Regenerative Medicine II FY18 appropriations were used to fund 16 modifications.
[4] Includes 2013-2015, 2018 Clinical Research Intramural Initiative (CRII) and 2010 Chiropractic Clinical Trials.
[5] CSI: Congressional Special Interest
[6] Includes 2016-2017 CRII.
[7] CDMRP manages the application receipt and review process for the USAMRDC Broad Agency Announcement. Proposals that are funded are counted in the program that provided the funding. Of the 114 applications received, CDMRP funded 33.

Appendix B: FY18-FY19

Table B-1. FY18-FY19 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
2018	**$4.0M** for Alcohol and Substance Abuse Research	**Withholds** USAMRDC: $57,975 SBIR/STTR: $135,000 **Management Costs** $128,500 3.38%	**Research** Consortium Award: 3,678,525
	Total: $4.0M	**$321,475**	**Total: $3,678,525**
2019	**$4.0M** for Alcohol and Substance Abuse Research	**Withholds** USAMRDC: $67,655 SBIR/STTR: $134,000 **Budgeted Management Costs** $265,000 7%	**Research** Budgeted Peer-Reviewed Research: $3,533,345
	Total: $4.0M	**$466,655**	**Total: $3,533,345**

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. FY18-FY19 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
2018	**$10M** for Amyotrophic Lateral Sclerosis Research	**Withholds** USAMRDC: $144,338 SBIR/STTR: $335,000 **Management Costs** $428,505 4.50%	**Research** Therapeutic Idea Award: $6,279,865 Therapeutic Development Award: $2,812,292
	Total: $10M	**Total: $907,843**	**Total: $9,092,157**
2019	**$10M** for Amyotrophic Lateral Sclerosis Research	**Withholds** USAMRDC: $169,138 SBIR/STTR: $335,000 **Budgeted Management Costs** $605,863 6%	**Research** Budgeted Peer-Reviewed Research: $8,890,000
	Total: $10M	**Total: $1,110,000**	**Total: $8,890,000**

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. FY18-FY19 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
2018	**$7.5M** for Autism Research	**Withholds** USAMRDC: $108,581 SBIR/STTR: $252,000 **Management Costs** $462,057 6.47%	**Research** Idea Development: $1,491,127.00 Clinical Trial Award: $4,472,366.00 Clinical Translational Research: $713,869.00
	Total: $7.5M	**Total:$822,638**	**Total: $6,677,362**
2019	**$7.5M** for Autism Research	**Withholds** USAMRDC: $126,840 SBIR/STTR: $252,000 **Budgeted Management Costs** $498,000 7%	**Research** Budgeted Peer-Reviewed Research: $6,623,160
	Total: $7.5M	**Total:$876,840**	**Total:$6,623,160**

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. FY18-FY19 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
2018	**$3.0M** for Bone Marrow Failure Research	**Withholds** USAMRDC: $43,499 SBIR/STTR: $100,000 **Management Costs** $135,957 4.76%	**Research** Idea Development Award - Early Career Investigator: $488,841 Idea Development Award - Established Investigator: 2,231,703
	Total: $3.0M	**Total: $279,456**	**Total: $2,720,544**
2019	**$3.0M** for Bone Marrow Failure Research	**Withholds** USAMRDC: $50,733 SBIR/STTR: $101,000 **Budgeted Management Costs** $191,268 7%	**Research** Budgeted Peer-Reviewed Research: $2,657,000
	Total: $3.0M	**Total: $343,000**	**Total: $2,657,000**

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. FY18-FY19 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
2018	**$130M** for Breast Cancer Research **$554,433** proceeds from the Stamp Out Breast Cancer Act	**Withholds** USAMRDC: $1,884,570 SBIR/STTR: $4,362,000 **Management Costs** $9,528,549 7.67%	**Research** Breakthrough Award Funding Level 1: $5,221,997 Breakthrough Award Funding Level 2: $25,680,390 Breakthrough Award Funding Level 1 Partnering PI Option: $10,000,670 Breakthrough Award Funding Level 2 Partnering PI Option: $17,292,039 Breakthrough Award Funding Level 3 Partnering PI Option: $22,278,213 Breakthrough Award Funding Level 4 Clinical Trial-Partnering PI Option: $11,082,668 Breakthrough Award - Funding Level 4 - Clinical Trial - Partnering PI Option: $9,099,284 Breakthrough Fellowship Award: $2,342,898 Expansion Award: $11,781,154
	Total: $130,554,433	**Total: $15,775,119**	**Total: $114,779,314**
2019	**$130M** for Breast Cancer Research **$211,924** proceeds from the Stamp Out Breast Cancer Act	**Withholds** USAMRDC: $2,198,683 SBIR/STTR: $4,361,000 **Budgeted Management Costs** $8,600,000 7%	**Research** Budgeted Peer-Reviewed Research: $114,840,318
	Total: $130,205,848	**Total: $15,159,683**	**Total: $114,840,318**

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 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	**$10.0M** for Chronic Pain Research	**Withholds** USAMRDC: $169,138 SBIR/STTR: $335,000 **Budgeted Management Costs** $663,000 7%	**Research** Budgeted Peer-Reviewed Research: $8,832,863
	Total: $10.0M	**Total: $1,167,138**	**Total: $8,832,863**

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 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	**$15.0M** for Combat Readiness Research	**Withholds** USAMRDC: $253,960 SBIR/STTR: $488,000 **Budgeted Management Costs** $1,000,000 7%	**Research** Budgeted Peer-Reviewed Research: $13,258,040
	Total: $15.0M	**Total: $1,741,960**	**Total: $13,258,040**

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-8. FY18-FY19 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
2018	**$3.2M** for Duchenne Muscular Dystrophy Research	**Withholds** USAMRDC: $46,395 SBIR/STTR: $107,000 **Management Costs** $106,384 3.49%	**Research** Investigator Initiated Research: $948,794 Investigator-Initiated Research Award - Optional Interdisciplinary Collaborator - Clinical Trial: $1,991,427
	Total: $3.2M	**Total: $259,779**	**Total: $2,940,221**
2019	**$3.2M** for Duchenne Muscular Dystrophy Research	**Withholds** USAMRDC: $54,128 SBIR/STTR: $107,000 **Budgeted Management Costs** $211,873 7%	**Budgeted Research** Budgeted Peer-Reviewed Research: $2,827,000
	Total: $3.2M	**Total: $373,000**	**Total: $2,827,000**

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-9. FY18-FY19 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
2018	**$7.5M** for Epilepsy Research	**Withholds** USAMRDC: $108,720 SBIR/STTR: $252,000 **Management Costs** $500,432 7.01%	**Research** Idea Development Award - Funding Level 1: $955,937 Idea Development Award - Funding Level 2: $2,848,139 Epilepsy Risk Factors Award: $146,170 Longitudinal Risk Factors Award: $2,688,602
	Total: $7.5M	**Total: $861,152**	**Total: $6,638,848**
2019	**$7.5M** for Epilepsy Research	**Withholds** USAMRDC: $126,840 SBIR/STTR: $252,000 **Budgeted Management Costs** $471,160 7%	**Research** Budgeted Peer-Reviewed Research: $6,650,000.00
	Total: $7.5M	**Total: $850,000**	**Total: $6,650,000**

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-10. FY18-FY19 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
2018	**$21M** for Gulf War Illness Research	**Withholds** USAMRDC: $304,237 SBIR/STTR: $668,000 **Management Costs** $712,456 3.56%	**Research** Clinical Consortium Award: $658,050 Clinical Trial Award: $1,180,691 Clinical Trial Award - Biorepository Contribution Option: $1,625,254 Gulf War Illness Epidemiology Research Award: $436,960 Investigator-Initiated Focused Research Award - Tier 1: $1,877,150 Investigator-Initiated Focused Research Award - Tier 2: $6,663,263 Investigator-Initiated Focused Research Award - Tier 2 - Biorepository Contribution Option: $2,017,095 Investigator Initiated Research Award: $334,820 Investigator-Initiated Research Expansion Award - Collaborative Option: $54,500 New Investigator Award: $123,575 New Investigator Award - Early Career Investigator: $1,575,559 New Investigator Award - New GWI Researcher: $2,058,871 Qualitative Research Award: $709,520
	Total: $21M	**Total: $1,684,693**	**Total: $19,315,307**
2019	**$22M** for Gulf War Illness Research	**Withholds** USAMRDC: $372,662.50 SBIR/STTR: $705,000 **Budgeted Management Costs** $1,422,338 7%	**Research** Budgeted Peer-Reviewed Research: $19,500,000.00
	Total: $22M	**Total: $2,500,000**	**Total: $19,500,000**

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-11. FY18-FY19 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
2018	**$10M** for Hearing Restoration Research	**Withholds** USAMRDC: $144,975 SBIR/STTR: $335,000 **Budgeted Management Costs** $399,327 4.19%	**Research** Focused Applied Research Award: $6,649,163 Focused Research Award: $3,750 Translational Research Award: $2,467,785
	Total: $10M	**Total: $879,302**	**Total: $9,120,698**
2019	**$10M** for Hearing Restoration Research	**Withholds** USAMRDC: $169,138 SBIR/STTR: $335,000 **Budgeted Management Costs** $645,863 7%	**Research** Budgeted Peer-Reviewed Research: $8,850,000
	Total: $10M	**Total: $1,150,000**	**Total: $8,850,000**

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-12. FY18-FY19 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
2018	**$50M** for Joint Warfighter Medical Research	**Withholds** USAMRDC: $725,074 SBIR/STTR: $1,626,000 **Budgeted Management Costs** $1,363,840 2.86%	**Budgeted Research** Peer-Reviewed Research: $46,285,086
	Total: $50M	**Total: $3,714,914**	**Total: $46,285,086**
2019	**$50M** for Joint Warfighter Medical Research	**Withholds** USAMRDC: $846,545 SBIR/STTR: $1,626,000 **Budgeted Management Costs** $3,227,455 7%	**Budgeted Research** Budgeted Peer-Reviewed Research: $44,300,000.00
	Total: $50M	**Total: $5,700,000**	**Total: $44,300,000**

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-13. FY18-FY19 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
2018	**$15M** for Kidney Cancer Research	**Withholds** USAMRDC: $217,190 SBIR/STTR: $503,000 **Budgeted Management Costs** $673,857 4.72%	**Research** Concept Award: $685,720 Idea Development Award - Early Career Investigator: $1,334,000 Idea Development Award- Established Investigator: $7,028,533 Physician Research Award: $657,303 Technology Development Award: $900,201 Translational Research Partnership Award: $3,000,196
	Total: $15M	**Total: $1,394,047**	**Total: $13,605,953**
2019	**$20M** for Kidney Cancer Research	**Withholds** USAMRDC: $337,995 SBIR/STTR: $686,000 **Budgeted Management Costs** $1,328,005 7%	**Research** Budgeted Peer-Reviewed Research: $17,648,000
	Total: $20M	**Total: $2,352,000**	**Total: $17,648,000**

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-14. FY18-FY19 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
2018	**$14M** for Lung Cancer Research	**Withholds** USAMRDC: $202,950 SBIR/STTR: $470,000 **Management Costs** $788,369 5.92%	**Research** Career Development Award: $856,250 Concept Award: $1,747,522 Idea Development Award - Established Investigator: $4,093,867 Idea Development Award - New Investigator Option: $1,152,234 Investigator-Initiated Translational Research Award: $1,880,467 Translational Research Partnership Award: $2,808,341
	Total: $14M	**Total: $1,461,319**	**Total: $12,538,681**
2019	**$14M** for Lung Cancer Research	**Withholds** USAMRDC: $236,775 SBIR/STTR: $470,000 **Budgeted Management Costs** $930,225 7%	**Research** Budgeted Peer-Reviewed Research: $12,363,000
	Total: $14M	**Total: $1,637,000**	**Total: $12,363,000**

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-15. FY18-FY19 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
2018	**$5M** for Lupus Research	**Withholds** USAMRDC: $72,394 SBIR/STTR: $168,000 **Budgeted Management Costs** $288,449 6.06%	**Research** Concept Award: $747,247 Impact Award: $3,723,910
	Total: $5M	**Total: $528,843**	**Total: $4,471,157**
2019	**$5M** for Lupus Research	**Withholds** USAMRDC: $84,560 SBIR/STTR: $168,000 **Budgeted Management Costs** $327,440 7%	**Research** Budgeted Peer-Reviewed Research: $4,420,000
	Total: $5M	**Total: $580,000**	**Total: $4,420,000**

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-16. FY19 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	**$10.0M** for Melanoma Research	**Withholds** USAMRDC: $169,138 SBIR/STTR: $335,000 **Budgeted Management Costs** $759,669 8%	**Research** Budgeted Peer-Reviewed Research: $8,736,194
	Total: $10.0M	**Total: $1,263,807**	**Total: $8,736,194**

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. FY18-FY19 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
2018	**$8M** for Military Burn Research	**Withholds** USAMRDC: $280,000 ABO 8110: $14,901 **Budgeted Management Costs** $273,216 3.55%	**Research** Broad Agency Announcement for Extramural Medical Research: $53,713 Burn Injuries Research Award - Funding Level 1: $141,480 Clinical Trial Award: $48,613 Clinical Trial Award - Research Level 2: $7,188,077
	Total: $8M	**Total: $568,117**	**Total: $7,431,883**
2019	**$8M** for Military Burn Research	**Withholds** USAMRDC: $140,000 **Budgeted Management Costs** $550,000 7%	**Research** Budgeted Peer-Reviewed Research: $7,310,000
	Total: $8M	**Total: $690,000**	**Total: $7,310,000**

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. FY18-FY19 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
2018	**$6.0M** for Multiple Sclerosis Research	**Withholds** USAMRDC: $86,199 SBIR/STTR: $201,000 **Management Costs** $344,483 6.03%	**Research** Exploration - Hypothesis Development Award: $874,469 Investigator-Initiated Research Award: $4,493,849
	Total: $6M	**Total: $631,682**	**Total: $5,368,318**
2019	**$6.0M** for Multiple Sclerosis Research	**Withholds** USAMRDC: $101,483 SBIR/STTR: $201,000 **Budgeted Management Costs** $397,518 7%	**Research** Budgeted Peer-Reviewed Research: $5,300,000
	Total: $6M	**Total: $700,000**	**Total: $5,300,000**

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-19. FY18-FY19 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
2018	**$15M** for Neurofibromatosis Research	**Withholds** USAMRDC: $525,000 ABO 8110: $26,129 **Management Costs** $559,026 3.87%	**Research** Clinical Consortium Award: $1,143,446 Clinical Trial Award: $1,243,540 Early Investigator Research Award: $968,075 Exploration-Hypothesis Development Award: $1,143,706 Investigator-Initiated Research Award: $6,274,481 New Investigator Award: $3,116,597
	Total: $15M	**Total: $1,110,155**	**Total: $13,889,845**
2019	**$15M** for Neurofibromatosis Research	**Withholds** USAMRDC: $262,500 **Budgeted Management Costs** $1,020,000 7%	**Research** Budgeted Peer-Reviewed Research: $13,717,500
	Total: $15M	**Total: $1,282,500**	**Total: $13,717,500**

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. FY18-FY19 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
2018	**$10M** for Orthotics and Prosthetics Outcomes Research	**Withholds** USAMRDC: $144,975 SBIR/STTR: $335,000 **Management Costs** $467,835 4.91%	**Research** Clinical Research Award - Funding Level 1: $695,161 Clinical Research Award - Funding Level 2: $4,473,374 Clinical Trial Award - Funding Level 1: $350,000 Clinical Trial Award - Funding Level 2: $3,533,655
	Total: $10M	**Total: $947,810**	**Total: $9,052,190**
2019	**$10M** for Orthotics and Prosthetics Outcomes Research	**Withholds** USAMRDC: $169,138 SBIR/STTR: $335,000 **Budgeted Management Costs** $665,000 7%	**Research** Budgeted Peer-Reviewed Research: $8,830,863
	Total: $10M	**Total: $1,169,138**	**Total: $8,830,863**

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. FY18-FY19 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
2018	**$20M** for Ovarian Cancer Research	**Withholds** USAMRDC: $289,799 SBIR/STTR: $671,000 **Management Costs** $751,599 3.95%	**Research** Clinical Development Award: $1,642,154 Investigator-Initiated Research Award: $5,490,033 Omics Consortium Development Award: $1,465,985 Outcomes Consortium Award: $2,067,451 Ovarian Cancer Academy - Early-Career Investigator Award: $3,310,146 Pilot Award: $4,311,832
	Total: $20M	**Total: $1,712,399**	**Total: $18,287,601**
2019	**$20M** for Ovarian Cancer Research	**Withholds** USAMRDC: $338,258 SBIR/STTR: $671,000 **Budgeted Management Costs** $1,290,743 7%	**Research** Budgeted Peer-Reviewed Research: $17,700,000
	Total: $20M	**Total: $2,300,000**	**Total: $17,700,000**

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-22. FY18-FY19 Parkinson'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
2018	**$16M** for Parkinson's Research	**Withholds** USAMRDC: $560,000 ABO 8110: $27,871 **Management Costs** $1,100,166 7.14%	**Research** Early Investigator Research Award: $1,359,718 Investigator-Initiated Research Award: $7,459,377 Investigator-Initiated Research Award-Partnering PI Option: $5,492,868
	Total: $16M	**Total: $1,688,037**	**Total: $14,311,963**
2019	**$16M** for Parkinson's Research	**Withholds** USAMRDC: $280,000 **Budgeted Management Costs** $1,070,000 7%	**Research** Budgeted Peer-Reviewed Research: $14,650,000
	Total: $16M	**Total: $1,350,000**	**Total: $14,650,000**

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-23. FY18-FY19 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
2018	**$15M** for Peer Reviewed Alzheimer's Research	**Withholds** USAMRDC: $217,453 SBIR/STTR: $503,000 **Management Costs** $848,670 5.94%	**Research** Convergence Science Research Award: $7,628,941 New Investigator Research Award: $2,356,757 Research Partnership Award: $3,445,179
	Total: $15M	**Total: $1,569,123**	**Total: $13,430,877**
2019	**$15M** for Peer Reviewed Alzheimer's Research	**Withholds** USAMRDC: $253,698 SBIR/STTR: $503,000 **Budgeted Management Costs** $943,303 7%	**Research** Budgeted Peer-Reviewed Research: $13,300,000
	Total: $15M	**Total: $1,700,000**	**Total: $13,300,000**

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-24. FY18-FY19 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
2018	**$80M** for Peer-Reviewed Cancer Research	**Withholds** USAMRDC: $1,159,740 SBIR/STTR: $2,684,000 **Management Costs** $4,593,282 6.03%	**Research** Adrenal Cancer: $2,173,005 Bladder Cancer: $8,646,118 Blood Cancers: $6,871,204 Brain Cancer: $2,923,889 Cancer in Children, Adolescents, and Young Adults: $6,421,258 Colorectal Cancer: $5,647,793 Immunotherapy: $6,740,930 Liver Cancer: $7,208,288 Lymphoma: $1,156,915 Melanoma and Other Skin Cancers: $8,441,462 Mesothelioma: $2,298,082 Myeloma: $2,209,601 Neuroblastoma: $1,482,192 Pancreatic Cancer: $4,686,286 Pediatric Brain Tumors: $2,454,279 Stomach Cancer: $1,594,630 Leukemia: $607,046
	Total: $80M	**Total: $8,437,022**	**Total: 71,562,978**
2019	**$90M** for Peer-Reviewed Cancer Research	**Withholds** USAMRDC: $1,521,643 SBIR/STTR: $3,049,000 **Budgeted Management Costs** $5,979,358 7%	**Research** Budgeted Peer-Reviewed Research: $79,450,000
	Total: $90M	**Total: $10,550,000**	**Total: $79,450,000**

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)
FY19 Peer Reviewed Cancer Research Program: The agreement provides $90,000,000 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 DOD. 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, cancer in children, adolescents, and young adults, colorectal cancer, immunotherapy, listeria vaccine for cancer, liver cancer, lymphoma, mesothelioma, neuroblastoma, pancreatic cancer, pediatric brain tumors, rare cancers, stomach cancer.

Table B-25. FY18-FY19 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
2018	**$330M** for Peer-Reviewed Medical Research	**Withholds** USAMRDC: $4,784,884 SBIR/STTR: $10,961,000 **Management Costs** $18,942,074 6.03%	**Research** Acute Lung Injury: $16,615,909 Antimicrobial Resistance: $12,128,967 Burn Pit Exposure: $1,472,838 Cardiomyopathy: $7,595,668 Cerebellar Ataxia: $1,200,486 Chronic Migraine and Post-Traumatic Headache: $10,229,280 Chronic Pain Management: $4,365,262 Congenital Heart Disease: $15,911,821 Diabetes: $28,038,544 Dystonia: $6,995,623 Eating Disorders: $8,248,817 Emerging Infectious Diseases: $2,538,663 Endometriosis: $9,227,629 Epidermolysis Bullosa: $2,991,032 "Focal Segmental Glomerulo-sclerosis": $9,132,639 Fragile X Syndrome: $2,211,363 Frontotemporal Degeneration: $2,265,505 Hepatitis B and C: $4,915,411 Immunomonitoring of Intestinal Transplants: $2,559,733 Inflammatory Bowel Diseases: $5,780,327 Interstitial Cystitis: $4,200,821 Lung Injury: $2,032,436 Malaria: $6,825,911 Metals Toxicology: $272,581 Mitochondrial Disease: $4,116,099 Musculoskeletal Disorders: $8,844,573 Myotonic Dystrophy: $3,030,725 Non-Opioid Pain Management: $4,876,772 Pancreatitis: $18,458,381 Pathogen-Inactivated Blood Products: $2,405,708 Post-Traumatic Osteoarthritis: $10,445,289 Pressure Ulcers: $910,033 Pulmonary Fibrosis: $6,351,845 Respiratory Health: $9,722,928 Rett Syndrome: $4,625,328 Rheumatoid Arthritis: $1,748,208 Sleep Disorders: $568,853 Sustained-Release Drug Delivery: $4,948,669 Tinnitus: $2,488,910 Tissue Regeneration: $6,119,111 Tuberculosis: $6,497,302 Vaccine Development for Infectious Disease: $27,207,249 Vascular Malformations: $4,188,793
	Total: $330M	**Total: $34,687,959**	**Total: $295,312,041**
2019	**$350M** for Peer-Reviewed Medical Research	**Withholds** USAMRDC: $5,920,408 SBIR/STTR: $11,691,000 **Budgeted Management Costs** $22,388,593 7%	**Research** Budgeted Peer-Reviewed Research: $310,000,000
	Total: $350M	**Total: $40,000,000**	**Total: $310,000,000**

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)
FY19 Peer Reviewed Medical Research Program: The agreement provides $310,000,000 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: acute lung injury, antimicrobial resistance, arthritis, burn pit exposure, cardiomyopathy, cerebellar ataxia, chronic migraine and post-traumatic headache, congenital heart disease, constrictive bronchiolitis, diabetes, dystonia, eating disorders, emerging infectious diseases, epidermolusis bullosa, focal segmental glomerulosclerosis, frontotemporal degeneration, Guillain-Barre syndrome, hepatitis B, hereditary angioedema, hydrocephalus, immunomonitoring of intestinal transplants, inflammatory bowel disease, interstitial cystitis, lung injury, metals toxicology, mitochondrial disease, musculoskeletal disorders, myotonic dystrophy, nanomaterials for bone regneration, nutrition optimization, pancreatitis, pathogen-inactivated blood products, polycystic kidney disease, post-traumatic osteoarthritis, pressure ulcers, pulmonary fibrosis, resilience training, respiratory health, Rett syndrome, rheumatoid arthritis, scleroderma, sleep disorders, spinal muscular atrophy, tinnitus, tissue regeneration, tuberculosis, vascular malformations, and women's heart disease.

Table B-26. FY18-FY19 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
2018	**$30M** for Peer-Reviewed Orthopedic Research	**Withholds** USAMRDC: $433,116 SBIR/STTR: $1,006,000 **Management Costs** $1,858,054 6.51%	**Research** Applied Research Award: $5,625,535 Applied Research Award - Funding Level 1: $43,180 Applied Research Award - Funding Level 2: $152,866 Clinical Translational Research Award: $6,907,160 Clinical Trial Award: $13,659,620 Integrated Clinical Trial Award: $314,470
	Total: $30M	**Total: $3,297,169**	**Total: $26,702,831**
2019	**$30M** for Peer-Reviewed Orthopedic Research	**Withholds** USAMRDC: $507,395 SBIR/STTR: $1,006,000 **Budgeted Management Costs** $1,990,000 7%	**Research** Budgeted Peer-Reviewed Research: $26,496,605
	Total: $30M	**Total: $3,503,395**	**Total: $26,496,605**

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. FY18-FY19 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
2018	**$100M** for Prostate Cancer Research	**Withholds** USAMRDC: $1,449,675 SBIR/STTR: $3,355,000 **Management Costs** $4,099,064 4.31%	**Research** Clinical Consortium Award - Clinical Research Site: $568,119 Clinical Consortium Award - Coordinating Center with a Clinical Research Site: $2,048,038 Clinical Consortium Research Site Award: $1,762,814 Early Investigator Research Award: $4,825,120 Health Disparity Fellowship Award: $1,430,014 Health Disparity Research Award - Established Investigator: $11,728,555 Health Disparity Research Award - New Investigator: $1,534,185 Idea Development Award: $175,294 Idea Development Award-Established Investigator: $33,637,555 Idea Development Award-New Investigator Option: $12,258,552 Idea Expansion Award: $3,489,983 Impact Award: $9,819,075 Pathology Resource Network Award: $1,856,963 Physician Research Award: $5,961,994
	Total: $100M	**Total: $8,903,739**	**Total: $91,096,261**
2019	**$100M** for Prostate Cancer Research	**Withholds** USAMRDC: $1,691,288 SBIR/STTR: $3,355,000 **Budgeted Management Costs** $6,600,000 7%	**Research** Budgeted Peer-Reviewed Research: $88,353,713
	Total: $100M	**Total: 11,646,287.50**	**Total: $88,353,713**

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. FY18-FY19 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
2018	**$12M** for Reconstructive Transplant Research	**Withholds** USAMRDC: $173,306 SBIR/STTR: $403,000 **Management Costs** $633,968 5.55%	**Research** Concept Award: $832,432 Investigator-Initiated Research Award: $6,960,653 Qualitative Research Award: $2,996,642
	Total: $12M	**Total: $1,210,274**	**Total: $10,789,727**
2019	**$12M** for Reconstructive Transplant Research	**Withholds** USAMRDC: $202,948 SBIR/STTR: $403,000 **Budgeted Management Costs** $794,053 7%	**Research** Budgeted Peer-Reviewed Research: $10,600,000
	Total: $12M	**Total: $1,400,000**	**Total: $10,600,000**

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-29. FY18-FY19 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
2018	**$30M** for Spinal Cord Injury Research	**Withholds** USAMRDC: $434,910 SBIR/STTR: $1,006,000 **Management Costs** $1,654,253 5.79%	**Research** Clinical Trial Award: $11,197,757 Investigator-Initiated Research Award: $4,336,973 Qualitative Research Award: $1,559,516 Translational Research Award: $9,810,591
	Total: $30M	**Total: $3,095,163**	**Total: $26,904,837**
2019	**$30M** for Spinal Cord Injury Research	**Withholds** USAMRDC: $507,395 SBIR/STTR: $1,006,000 **Budgeted Management Costs** $1,990,000 7%	**Research** Budgeted Peer-Reviewed Research: $26,496,605
	Total: $30M	**Total: $3,503,395**	**Total: $26,496,605**

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. FY18-FY19 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
2018	**$5M** for Tick-Borne Disease Research	**Withholds** USAMRDC: $72,379 SBIR/STTR: $168,000 **Management Costs** $455,834 9.58%	**Research** Career Development Award: $905,150 Idea Award - Established Investigator: $230,810 Investigator Initiated Research Award: $3,167,827
	Total: $5M	**Total: $696,213**	**Total: $4,303,787**
2019	**$5M** for Tick-Borne Disease Research	**Withholds** USAMRDC: $84,560 SBIR/STTR: $168,000 **Budgeted Management Costs** $327,440 7%	**Research** Budgeted Peer-Reviewed Research: $4,420,000
	Total: $5M	**Total: $580,000**	**Total: $4,420,000**

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-31. FY18-FY19 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
2018	**$6M** for Tuberous Sclerosis Complex Research	**Withholds** USAMRDC: $86,985 SBIR/STTR: $201,000 **Management Costs** $388,329 6.80%	**Research** Clinical Translational Research Award: $227,882 Exploration - Hypothesis Development Award: $1,078,978 Idea Development Award - Established Investigator: $1,817,982 Idea Development Award - New Investigator: $2,198,844
	Total: $6M	**Total: $676,314**	**Total: $5,323,686**
2019	**$6M** for Tuberous Sclerosis Complex Research	**Withholds** USAMRDC: $101,483 SBIR/STTR: $201,000 **Budgeted Management Costs** $397,518 7%	**Research** Budgeted Peer-Reviewed Research: $5,300,000
	Total: $6M	**Total: $700,000**	**Total: $5,300,000**

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-32. FY18-FY19 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
2018	**$15M** for Vision Research	**Withholds** USAMRDC: $217,455 SBIR/STTR: $503,000 **Management Costs** $683,611 4.79%	**Research** Clinical Trial Award: $37,622 Expansion Award: $3,036,297 Focused Translational Team Science Award: $5,863,702 Investigator-Initiated Research Award: $4,655,613 Technology/Therapeutic Development Award: $2,700
	Total: $15M	**Total: $1,404,066**	**Total: $13,595,934**
2019	**$20M** for Vision Research	**Withholds** USAMRDC: $337,995 SBIR/STTR: $686,000 **Budgeted Management Costs** $1,276,005 7%	**Research** Budgeted Peer-Reviewed Research: $17,700,000
	Total: $20M	**Total: $2,300,000**	**Total: $17,700,000**

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-33. FY18 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
2018	**$40.4M f**or Defense Medical Research and Development from the Guidance for the Development of the Force Funding	**Management Costs** $219,860 0.47%	**Research** Medical Simulation and Information Sciences Awards: $1,294,093 Military Infectious Diseases Awards: $5,670,000 Military Operational Medicine Awards: $70,764 Combat Casualty Care Awards: $11,881,928 Clinical and Rehabilitative Medicine Awards: $17,646,713 Accelerating Innovation in Military Medicine Research Award: $3,736,109
	Total: $40.4M	**Total: $219,860**	**Total: $40,299,607**

Percent of management costs=management costs/(appropriation-withholds)

Table B-34. FY18 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
2018	**$100.7M** for Defense Medical Research and Development from the Guidance for the Development of the Force Funding	**Management Costs** $12,589,268 11.20%	**Research** Medical Simulation and Information Sciences Awards: $8,390,474 Military Infectious Diseases Awards: $2,022,708 Military Operational Medicine Awards: $3,589,093 Combat Casualty Care Awards: $34,727,559 Clinical and Rehabilitative Medicine Awards: $34,040,661 Accelerating Innovation in Military Medicine Research Award: $5,337,449
	Total: $100.7M	**Total: $12,589,268**	**Total: $88,107,944**

Percent of management costs=management costs/(appropriation-withholds)

Table B-35. FY18 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
2018	**$60.9M** for Psychological Health and Traumatic Brain Injury Research	**Management Costs** $5,145,494 8%	**Research** Broad Agency Announcement for Extramural Medical Research: $6,035,875 Complex Traumatic Brain Injury Rehabilitation Research Award - Clinical Trial Award: $4,708,166 Complex Traumatic Brain Injury Rehabilitation Research Award - Funding Level 2: $50,000 Complex Traumatic Brain Injury Rehabilitation Research-Clinical Research Award: $7,439,437 Complex Traumatic Brain Injury Rehabilitation Research-Clinical Trial Award: $1,777,332 Complex Traumatic Brain Injury Rehabilitation Research-Clinical Trial Development Award: $399,999 Joint Warfighter Medical Research Program: $147,500 Long-Term Impact of Military-Related Brain Injury Consortium Award: $4,978,043 Medical Research Award: $2,849,180 Medical Research Award - Research Including Clinical Trial: $7,443,206 Neurosensory and Rehabilitation Research Award - Applied Research Option: $2,342 Precision Trauma Care Research Award: $6,765,873 Precision Trauma Care Research Award - Clinical Trial: $2,899,241 Prolonged Field Care Research Award - Funding Level 1 - Clinical Research: $4,000 Prolonged Field Care Research Award - Funding Level 2 - Preclinical Research: $100,080 Psychological Health Research Award: $69,347 Resilience and Readiness Optimization/Enhancement Translational Research Award: $7,297,469 Traumatic Brain Injury/ Post-Traumatic Stress Disorder - Clinical Trial Award: $200,482 Trauma Resiliency Immersive Adaptive Gaming Environment Award: $2,577,993
	Total: $60.9M	**Total: $5,145,494**	**Total: $55,745,566**

Percent of management costs=management costs/(appropriation-withholds)

Table B-36. FY2018 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
2018	**$9.50** for Armed Forces Institute of Regenerative Medicine	**Management Costs**	**Research** Focus Area Research: $9,466,003
	Total: $9.5M		**Total: $9,466,003**

Percent of management costs=management costs/(appropriation-withholds)

Table B-37. FY2018 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
2018	**$7.7M** for Small Business Innovation Research/Small Business Technology Transfer Research	**Management Costs**	**Research** Small Business Innovation Research: $7,196,984 Small Business Technology Transfer: $522,088
	Total: $7.7M	**Total:**	**Total: $7,719,072**

Percent of management costs=management costs/(appropriation-withholds)

Table B-38. FY18 Clinical Research Intramural Initiative
CDMRP Executed Funds, Management Costs, and Execution of Investment Strategy

Fiscal Year	CDMRP Executed Funds	Management Costs	Investment Strategy
2018	**$13.80** for Clinical Research Intramural Initiative	Infrastructure Support Services: $10,735,174	Health Services Research Award - Intramural: $158,500 Precision Medicine Research Award - Intramural - Research Level 1: $48,000 Precision Medicine Research Award - Intramural - Research Level 2: $906,432 Precision Medicine Research Award - Intramural - Research Level 3: $168,000 Military Performance Optimization Research Award: $596,000 Military Performance Optimization Research Award - Clinical Trial: $301,000 Military Women's Health Research Award: $859,000
	Total: $13.80	**Total: $10,735,174**	**Total: $3,036,932.00**

Percent of management costs=management costs/(appropriation-withholds)

Appendix C: Breast Cancer Research Semipostal Awards FY99–FY18

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	Quiyin 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	University of South Florida	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

[1]Total award amount was $404,176; remaining funds were from the FY99 BCRP.

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	International Agency for Cancer Research	Fatty Acid Synthesis Gene Variants and Breast Cancer Risk: A Study within the European Prospective Investigation into Cancer and Nutrition (EPIC)
	Paul Yaswen	$508,680	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
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?

[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.

Fiscal Year	Principal Investigator	Amount	Institution	Proposal Title
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]	University of Texas, at Austin	Noninvasive Label-Free Detection of Micrometastases in the Lymphatics with Ultrasound-Guided Photoacoustic Imaging
FY14	Dan Shu	$364,343	University of Kentucky	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
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

[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.

Appendix D: Acronyms

AD ..... Alzheimer's disease
ADNI ..... Alzheimer's Disease Neuroimaging Initiative
ADRD ..... AD and related dementia
AFIRM ..... Armed Forces Institute of Regenerative Medicine
ALS ..... amyotrophic lateral sclerosis
ALSRP ..... Amyotrophic Lateral Sclerosis Research Program
AR ..... androgen receptor
ARP ..... Autism Research Program
AR-V7 ..... androgen receptor splice variant 7
ASADRP ..... Alcohol and Substance Abuse Disorders Research Program
ASD ..... autism spectrum disorder
ASUDs ..... alcohol and substance use disorders
AUD ..... alcohol use disorder
B ..... billion
BAA ..... Broad Agency Announcement
BADER ..... Bridging Advanced Developments for Exceptional Rehabilitation
BBRAIN ..... Boston Biorepository, Recruitment, and Integrative Network
BCRP ..... Breast Cancer Research Program
BCRS ..... Breast Cancer Research Semipostal
BMF ..... bone marrow failure
BMFRP ..... Bone Marrow Failure Research Program
BOP ..... blast overpressure
BRCA2 ..... breast cancer gene 2
BU ..... Boston University
CAP ..... Consortium to Alleviate PTSD
CARE ..... Concussion Assessment, Research, and Education
CCCRP ..... Combat Casualty Care Research Program
CDEs ..... Common Data Elements
CDMRP ..... Congressionally Directed Medical Research Programs
CEBPD ..... CCAAT/enhancer-binding protein delta
CENC ..... Chronic Effects of Neurotrauma Consortium
CHP ..... collagen hybridizing peptide
CNV ..... corneal neovascularization
CPMRP ..... Chronic Pain Management Research Program
CRC ..... Concussion Research Consortium
CRII ..... Clinical Research Intramural Initiative
CRMRP ..... Clinical and Rehabilitative Medicine Research Program
CRRP ..... Combat Readiness-Medical Research Program
CsA ..... cyclosporinA
CSI ..... Congressional Special Interest
CURE ..... Citizens United for Research in Epilepsy
DARPA ..... Defense Advanced Research Projects Agency
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
DMRDP ..... Defense Medical Research and Development Program
DOD ..... Department of Defense
DTCs ..... Dormant Disseminated Tumor Cells
DUE DARE ..... Dense Urban Environment Dosimetry for Actionable Information and Recording Exposure
eBRAP ..... Electronic Biomedical Research Application Portal
ECIs ..... Early Career Investigators
EGS ..... Electronic Grants System
EPA ..... Environmental Protection Agency
ER ..... estrogen receptor positive
ERP ..... Epilepsy Research Program
ET ..... endotracheal tube
ETI ..... endotracheal intubation
FA ..... Fanconi anemia
FDA ..... US Food and Drug Administration
FIHET ..... Federal Interagency Health Equity Team
FITBIR ..... Federal Interagency Traumatic Brain Injury Research
FODMAPs ..... Fermentable Oligo-, Di- and Mono-saccharides and Polyols
FTTSA ..... Focused Translational Team Science Award
FY ..... fiscal year
GI ..... gastrointestinal
GLP-1 ..... Glucagonlike Peptide-1
GLP-1R ..... glucagon-like peptide-1 receptor
GMP ..... good manufacturing practice

GWI ..... Gulf War Illness
GWICTIC ..... Gulf War Illness Clinical Trials and Interventions Consortium
GWIRP ..... Gulf War Illness Research Program
HCC ..... hepatocellular carcinoma
HDAC ..... histone deacetylase
HGSC ..... high-grade serous carcinomas
Hh ..... hedgehog
HHS ..... US Department of Health and Human Services
HITI ..... Health Information Technologies/Informatics
HPFS ..... Health Professionals Follow-Up Study
HR ..... homologous recombination
HRRP ..... Hearing Restoration Research Program
HSC ..... hematopoietic stem cell
IACC ..... Interagency Autism Coordinating Committee
ICB ..... Immune Checkpoint Blockade
ICIs ..... immune checkpoint inhibitors
IDA ..... Idea Development Award
IOM ..... Institute of Medicine
IOP ..... intraocular pressure
IRF5 ..... interferon regulatory factor 5
ITN ..... Institute for Translational Neuroscience
JPCs ..... Joint Program Committees
JWMRP ..... Joint Warfighter Medical Research Program
KCRP ..... Kidney Cancer Research Program
LCRP ..... Lung Cancer Research Program
LITES ... Linking Investigations in Trauma and Emergency Services
LP ..... luminal progenitor
LRP ..... Lupus Research Program
M ..... million
MAST ..... Medical Assist Support Technologies
MBRP ..... Military Burn Research Program
MBV ..... matrix-bound nanovesicles
mCRPC ..... metastatic castration resistant prostate cancer
MDD ..... Materiel Development Decision
MDDT ..... Medical Device Development Tools
MDSs ..... Myelodysplastic syndromes
METRC ..... Major Extremity Trauma Research Consortium
MIDRP ..... Military Infectious Diseases Research Program
MLKIs ..... multiple ligament knee injuries
MM ..... Multiple Myeloma
MOBI ..... mobile brain/body imaging
MOMRP ..... Military Operational Medicine Research Program
MPRTS ..... Mirasol Pathogen Reduction Technology System
MR ..... Mineralocorticoid receptor
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
mTBI ..... mild traumatic brain injury
MTFs ..... Military Treatment Facilities
MTT ..... Microbiota Transfer Therapy
NAC ..... N-acetylcysteine
NAPA ..... National Alzheimer's Project Act
NASA ..... National Aeronautics and Space Administration
NBWT ..... Narrowing Beam Walking Test
NCAA ..... National Collegiate Athletic Association
NEPC ..... neuroendocrine prostate cancer
NETs ..... Neutrophil Extracellular Traps
NF ..... neurofibromatosis
NFCTC ..... Neurofibromatosis Clinical Trials Consortium
NFκB ..... nuclear factor kappa B
NFRP ..... Neurofibromatosis Research Program
NHS ..... Nurses' Health Study
NIH ..... National Institutes of Health
NSAID ..... nonsteroidal anti-inflammatory drug
NSCLC ..... non-small cell lung cancer
NSF ..... National Science Foundation
NSU ..... Nova Southeastern University
OASD(HA) ..... Office of the Assistant Secretary of Defense for Health Affairs
OCA ..... Ovarian Cancer Academy
OCRP ..... Ovarian Cancer Research Program's
OPORP .. Orthotics and Prosthetics Outcomes Research Program
ORP ..... Office of Research Protections
PA ..... Program Announcement
PADs ..... Program Area Directorates
PASA ..... Pharmacotherapies for Alcohol and Substance Abuse
PCBN ..... Prostate Cancer Biorepository Network
PCCTC ..... Prostate Cancer Clinical Trials Consortium
PCRP ..... Prostate Cancer Research Program
PD ..... Parkinson's disease
PH/TBIRP ..... Psychological Health and Traumatic Brain Injury Research Program
PI ..... Principal Investigator
PMC ..... Pain Management Collaboratory
PMCA ..... protein misfolding cyclic amplification
PNES ..... psychogenic non-epileptic seizures
PNS ..... Peripheral nerve stimulation
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
PRP ..... Parkinson's Research Program
PSA ..... prostate specific antigen
PS+ASD ..... Project SEARCH Plus ASD Supports
PTE ..... post-traumatic epilepsy
PTS ..... post-traumatic stress
PTSD ..... post-traumatic stress disorder
RA ..... Rheumatoid arthritis

RAA ..... Renin-Angiotensin-Aldosterone
R&A ..... Review and Analysis
R&D ..... research and development
Rb1 ..... retinoblastoma
RD ..... related dementias
RDT&E ..... Research, Development, Test, and Evaluation
RDTRA ..... Rapid Development and Translational Research Award
RFI ..... request for information
RGCs ..... Retinal ganglion cells
RHERP ..... Radiation Health Effects Research Program
RMA ..... Red meat allergy
rTMS ..... Repetitive Transcranial Magnetic Stimulation
RTRP ..... Reconstructive Transplant Research Program
SABR ..... stereotactic ablative radiotherapy
SBIR ..... Small Business Innovation Research
SCIRP ..... Spinal Cord Injury Research Program
SDP ..... silk-derived protein
SGNs ..... spiral ganglion neurons
SLE ..... Systemic lupus erythematosus
SSPs ..... Sessile Serrated Polyps
STaR ..... Surgical Timing and Rehabilitation
STIC ..... serous tubal intraepithelial carcinoma
STTR ..... Small Business Technology Transfer
TAPTE ..... Team Approach to the Prevention and Treatment of Post-Traumatic Epilepsy
TBDs ..... tick-borne diseases
TBDRP ..... Tick-Borne Disease Research Program
TBI ..... traumatic brain injury
TCRP ..... Trauma Clinical Research Program
TED ..... TBI Endpoints Development
TET1 ..... Ten-Eleven Translocation protein 1
TLK2 ..... Tousled-Like Kinase 2
TMR ..... Targeted muscle reinnervation
TON ..... traumatic optic neuropathy
TRACK-TBI ..... Transforming Research and Clinical Knowledge in TBI
TRIAGE ..... Trauma Resiliency Immersive Adaptive Gaming Environment
Trks ..... tropomyosin receptor kinases
TRL ..... Technology Readiness Level
TSC ..... Tuberous sclerosis complex
TubA ..... Tubastatin A
ULiSSES ..... Universal Limb Stasis System for Extended Storage
USAISR ..... US Army Institute of Surgical Research
USAMRAA ..... US Army Medical Research Acquisition Activity
USAMRDC ..... US Army Medical Research and Development Command
USDA ..... US Department of Agriculture
USU ..... Uniformed Services University
UV ..... ultraviolet
VA ..... US Department of Veterans Affairs
VCA ..... vascularized composite allotransplantation
VRP ..... Vision Research Program
VSs ..... vestibular schwannomas
WBCs ..... white blood cells
WRNMMC ..... Walter Reed National Military Medical Center

For more information, visit: http://cdmrp.army.mil
or contact us at:
usarmy.detrick.medcom-cdmrp.mbx.cdmrp-public-affairs@mail.mil
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