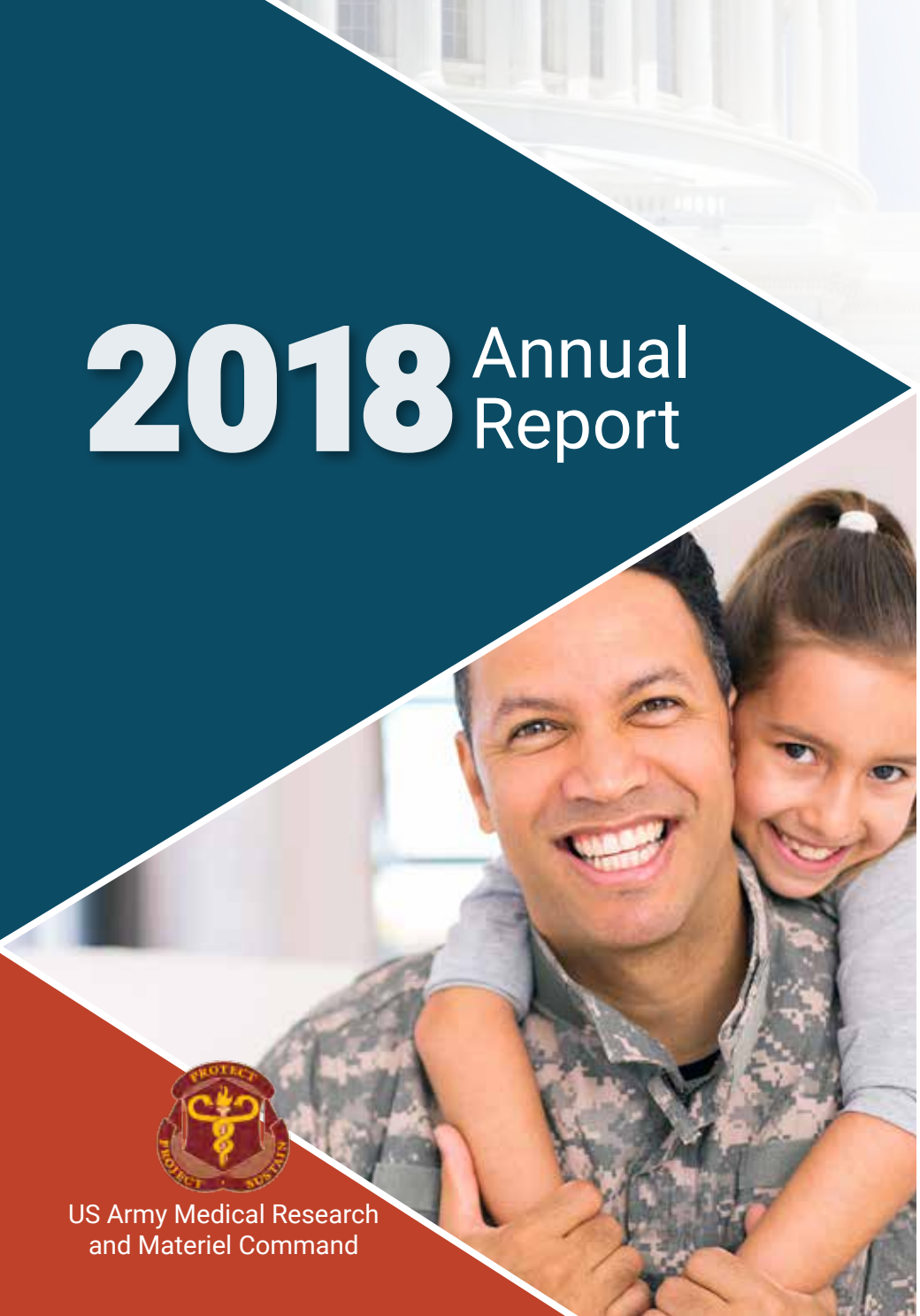
CDMRP
Department of Defense

Congressionally Directed Medical Research Programs

2018 Annual Report



US Army Medical Research and Materiel Command

LETTER FROM THE DIRECTOR

For nearly five years, I have had the honor of serving as the Director of the Congressionally Directed Medical Research Programs (CDMRP). Over these years, I have witnessed unparalleled commitment to advancing medical research by the CDMRP organization.

This annual report highlights the groundbreaking medical research that CDMRP has focused on through fiscal year 2018 (FY18). In an effort to remain transparent with our audience and stakeholders, we have developed this report to share program information, funding profiles, data pertaining to research projects awarded, and specific highlights for each of the research programs.

Through dynamic partnerships, we are able to team with scientists, consumers, academia and private industry to develop the most innovative and impactful medical advancements.

During the summer of FY18, leadership will transition as COL Stephen Dalal assumes the role of CDMRP Director. I look forward to witnessing the continued successes of CDMRP, as these major advances in medical research greatly affect our Service members, Veterans and the American public.

I have no doubt CDMRP will continue working towards transforming healthcare through advanced and cogent research.

Colonel Wanda L. Salzer, MD, MHSc,
US Air Force Medical Corps
Director, CDMRP

Department of Defense
US Army Medical Research and Materiel Command
Congressionally Directed Medical Research Programs
Annual Report
September 30, 2018

Congressionally Directed Medical Research Programs
ATTN: MCMR-CD
1077 Patchel Street, Fort Detrick, MD 21702-5024

Phone: 301-619-7071 — Fax: 301-619-7796 — http://cdmrp.army.mil

TABLE OF CONTENTS

Introduction

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.

HISTORY AND OVERVIEW

The origins of CDMRP reach back to 1992 when Congress first appropriated funds targeted specifically for breast cancer research. Since that time, additional research programs and topics have been added by Congress, and CDMRP has evolved into a global funding organization that fosters novel approaches to biomedical research in response to the expressed needs of its stakeholders. CDMRP fosters novel approaches to biomedical research in response to the expressed needs of the American public, the military, and Congress. CDMRP manages individual programs for cancer research, military medical 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 through innovative and impactful research that it funds. CDMRP implements the investment of congressionally directed dollars provided to fund groundbreaking, high-impact, meritorious research that

FISCAL YEAR 2018

CDMRP continued in FY18 providing management and oversight for its 30 research programs. In FY18, congressional appropriations increased for some programs. Additionally, the three new programs from FY17, the Hearing Restoration Research Program (HRRP; page 50), the Kidney Cancer Research Program (KCRP; page 54), and the Lupus Research Program (LRP; page 58) were also continued in FY18. The research funding managed by CDMRP over the last 10 years is shown in Figure 1.

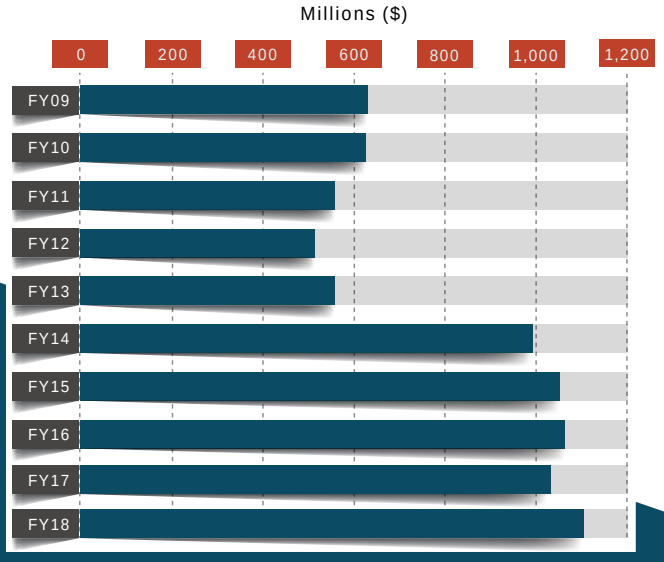


Figure 1. FY09–FY18 Research Funding

targets critical gaps. CDMRP also provides support for the management of core dollars (presidential budget) directed at both intramural and extramural military medical research portfolio areas.

CDMRP is located within the Department of Defense (DOD) US Army Medical Research and Materiel Command (USAMRMC). USAMRMC's mission is to responsively and responsibly create, develop, deliver, and sustain medical capabilities for the Warfighter by leading the advancement of military medicine, which is achieved through innovative management and efficient execution of allocated funding (read more about USAMRMC under Military Partnerships on page 12). Since its first appropriation of congressional funding in FY92, CDMRP has been responsible for managing more than $12.0 billion (B) in appropriations.

MAJOR UNDERTAKINGS IN FY18 ARE SUMMARIZED ON THE FOLLOWING PAGES

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 U.S. Army Medical Research and Development Command," 1993).

In 2014 the Senate Committee on Appropriations, Senate Report Number 113-211, 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 and respects 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 their 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 program Vision Setting meetings and updated as needed.

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 USAMRMC 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 (MHS) 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), USAMRMC, the US Army Medical Research Acquisition Activity (USAMRAA), the Special Operations Command, and CDMRP. In response to 146 FY17 funding opportunities, eBRAP received and processed over 12,437 pre-applications and over 7,312 full applications. During FY18, eBRAP is managing about 121 funding opportunities, with pre-application and full application receipts extending from June 2018 through March 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.
- 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.
- Provides functionality to the military medical community by directly accepting DOD intramural application submissions, which is not supported by Grants.gov.
- Has multi-user functionality allowing eBRAP to be easily customized for use by other organizations.
- Interfaces directly with Grants.gov for retrieval, processing, and administrative review of extramural applications.
- Provides "plug and play" pre-application component that provides modules to accommodate the varying needs of each Program Announcement (PA).
- 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 to Grants.gov).
- Provides capability to communicate with the research community both on a one-to-one basis and in batches and uses milestone-triggered automated delivery of communications to the research community.
- Is responsive to Contracting, Human Use, and Animal Use regulations.
- 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 is designed to focus 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 workflows 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 USAMRMC offices, including Acquisitions (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.
- Integrated processes include award, program, and financial management. Program evaluation is incorporated into EGS to allow for mining of data for analysis of outcomes and products.
- System-to-system interfaces allow transfer of data between USAMRMC, DOD partner organizations, and contractors that support various activities.
- Research outcomes and findings are captured and categorized in customized modules for analysis in program evaluation efforts, interaction with funded investigators, and reporting to stakeholders.
- Award data in EGS are automatically made publicly available nightly via the CDMRP website, in which users can view project details including abstracts and publications.
- 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 USAMRMC agencies.
- Recent enhancements allow the 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.

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 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 FY17–FY18 programs managed and/or supported by CDMRP can be found within the program pages in this Annual Report, beginning on page 31. As detailed in Table 1, CDMRP successfully completed obligation of FY17 appropriations across 31 programs encompassing 944 new research awards. In addition, in FY18, CDMRP initiated the management of $979.0 million (M) across 30 programs.

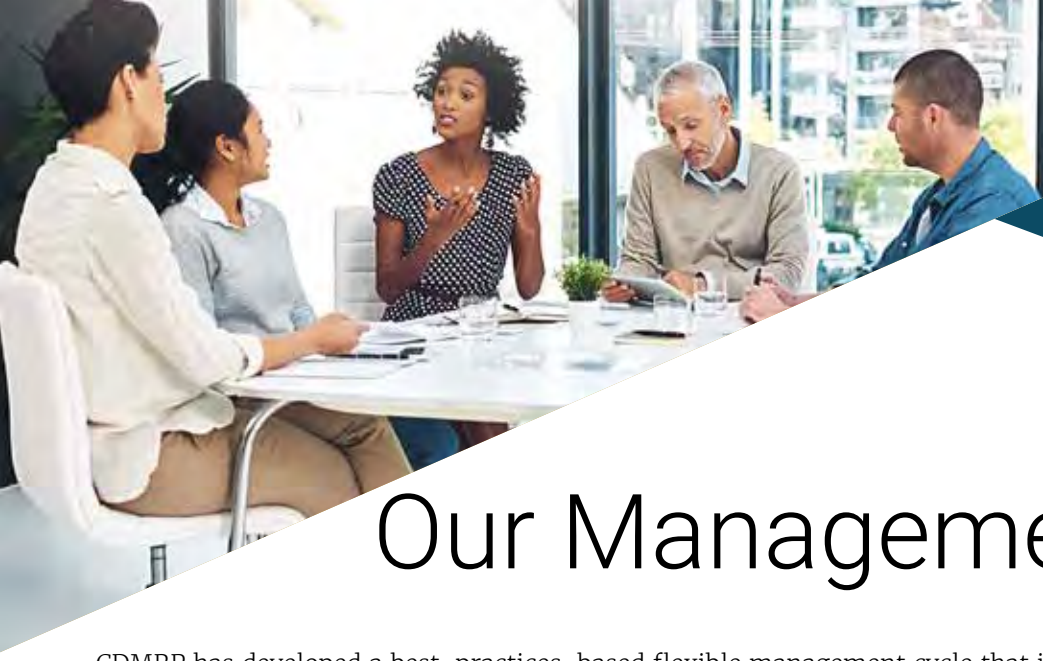
Table 1. CDMRP Programs, Appropriations, and Applications Received and Awarded in FY17-FY18

Research Programs Managed by the CDMRP	FY17				FY18	
	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	6	2		$4.0	
Amyotrophic Lateral Sclerosis	$7.5	55	8		$10.0	72
Autism	$7.5	78	11		$7.5	71
Bone Marrow Failure	$3.0	27	4		$3.0	32
Breast Cancer	$120.0	1,671	100	2	$130.0	911
Breast Cancer Research Semipostal(1)	$0.6			2	$0.6	
Duchenne Muscular Dystrophy	$3.2	33	4		$3.2	
Epilepsy	$7.5	37	13		$7.5	43
Gulf War Illness	$20.0	45	13	11	$21.0	37
Hearing Restoration	$10.0	23	7		$10.0	7
Joint Warfighter Medical(2)	$50.0		1	25	$50.0	46
Kidney Cancer	$10.0	244	22		$15.0	197
Lung Cancer	$12.0	333	27		$14.0	374
Lupus	$5.0	126	13		$5.0	98
Military Burn	$8.0	23	4	2	$8.0	
Multiple Sclerosis	$6.0	51	9		$6.0	57
Neurofibromatosis	$15.0	65	20	2	$15.0	87
Orthotics and Prosthetics Outcomes	$10.0	39	6		$10.0	37
Ovarian Cancer	$20.0	189	26	1	$20.0	168
Parkinson's	$16.0	137	16	1	$16.0	78
Peer Reviewed Alzheimer's	$15.0	99	18	1	$15.0	80
Peer Reviewed Cancer	$60.0	524	90		$80.0	823
Peer Reviewed Medical	$300.0	1,336	189	24	$330.0	1,426
Peer Reviewed Orthopaedic	$30.0	194	19	4	$30.0	57
Prostate Cancer	$90.0	710	108	12	$100.0	504
Reconstructive Transplant	$12.0	167	20	4	$12.0	150
Spinal Cord Injury	$30.0	140	27	1	$30.0	124
Tick-Borne Disease	$5.0	43	6	1	$5.0	39
Tuberous Sclerosis	$6.0	44	8	1	$6.0	56
Vision	$15.0	116	6	3	$15.0	
Additional Supported DOD Programs/Projects						
Armed Forces Institute of Regenerative Medicine II	$13.6			39	$9.5	
Centers of Excellence	$3.4			2	$2.6	
Defense Medical Research and Development	$112.4	563	59	86	$97.6	105
Defense Medical Research and Development CSI Restoral	$46.7		30	16	$20.5	
Psychological Health/Traumatic Brain Injury	$86.8	80	30	24	$47.3	7
Small Business Innovation Research/Small Business Technology Transfer	$21.8	50	28	5	$2.0	15
Trauma Clinical	$10.0			1	$10.0	
Other Submission Processes						
USAMRMC - Broad Agency Announcement(3)		125				117
Total	**$1,193.0**	**7,373**	**944**	**270**	**$1,168.3**	**5,818**

(1) Breast Cancer Semipostal funds applications received and reviewed by the BCRP.

(2) Joint Warfighter Medical Execution Management Breakdown: 1 award and 25 mods managed by CDMRP; 0 awards and 0 mods managed by USAMMDA; and 0 awards and 0 mods managed by USAMMA.

(3) CDMRP manages the application receipt and review process for the USAMRMC Broad Agency Announcement (BAA). Funded proposals that are managed by CDMRP are counted in the program that provided the funding. Of the 125 applications received, CDMRP funded 38.



Our Management Cycle

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 public. Under the leadership of a CDMRP Program Manager, each program follows the management cycle described in detail on the following pages. Each step in the management cycle is depicted in Figure 2 and discussed in detail in this section.

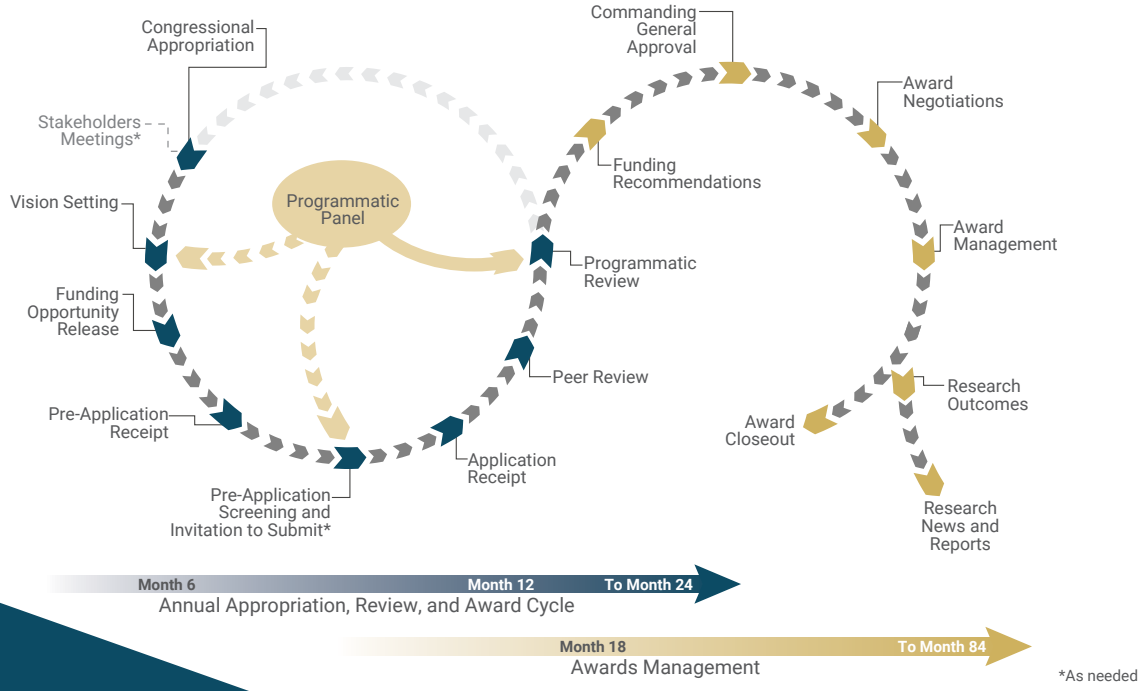


Figure 2. Program Management Cycle

FUNDING PROCESS

CDMRP is funded via annual congressional legislation known as the Defense Appropriations Act. For most programs, the DOD sends a multi-year budget request to Congress in the form of the President's Budget. However, dollars for CDMRP are not considered part of the DOD's core mission and are therefore not included in the DOD's requested budget. Rather, the dollars to fund CDMRP are added every year during the budget approval cycle by members of the House or Senate primarily in response to requests by consumer advocates and disease survivors.

1 Congressional Appropriation, Core Dollars, and Receipt of Funds

Funds for CDMRP programs are added annually to the DOD appropriation by Congress in a direct 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 through USAMRMC for military medical research that is funded from the President's Budget (core dollars). Over the years, CDMRP has been one of the main organizations within USAMRMC to support management for these funds.

2 Stakeholders Meeting

A Stakeholders meeting is held at the initiation of a new program and periodically thereafter to survey the research landscape and identify important areas of gaps and opportunities to scientists and consumers. 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 an 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, and the military, as well as consumers, to determine the program's goals and the award mechanisms to be offered. Based on the discussions, the vision setting process concludes with 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 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 participated in vision setting.

4 Program Announcements and Broad Agency Announcements

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

5 Application 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 FY17, CDMRP received 10,327 pre-proposals that, after screening and invitation, resulted in 4,012 full applications received. In addition, CDMRP received 2,503 full applications from mechanisms that required a letter of intent, for a total of 6,515 full applications received in this fiscal year.

On October 1, 2014, CDMRP began oversight of the receipt and review of submissions to the USAMRMC 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 USAMRMC and the DHA. These areas of interest are determined annually by the USAMRMC PADs/JPCs in response to evolving research priorities and knowledge gaps. For FY18, 224 pre-applications and 122 full applications were submitted to the BAA process and forwarded to the USAMRMC PADs/JPCs for programmatic decisions.

Table 2. Number of Submissions Received October 1, 2017-September 30, 2018, across FY17-FY18 Programs

Pre-Application Submissions	
Pre-proposals screened	7,325
Letters of intent received	3,002
Total pre-applications received	10,327
Full Application Submissions	
Full applications from invitations	4,012
Full applications from letters of intent	2,503
Total full applications	6,515

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 most recent 2016 report. The two-tier review process includes both peer review and programmatic review. The goal is to give every application a fair and balanced review, taking steps to ensure that conflicts of interest do not influence the process and the needs of the Warfighter and the general public are taken into account. Additional details regarding the two tiers of review can be accessed on the CDMRP website at http://cdmrp.army.mil/about/2tierrevprocess.shtml.

Peer Review: Peer review is a criteria-based process where applications are evaluated based on their scientific and technical merit. The peer review panel evaluates each application based on the review criteria outlined in the PA or BAA and rates the various criteria numerically or adjectivally. Each application is evaluated for its own 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.

Programmatic Review: After applications have been peer reviewed, they go through a criteria-based review by a Programmatic Panel comprised of experts including scientists, clinicians, military members, and/or consumers. At the programmatic review level, the Programmatic Panel uses the criteria published in the PA or BAA (i.e., programmatic relevance, portfolio balance, military impact, and scientific merit, etc.) in a comparison-based assessment of submitted applications. The product of Programmatic Review is a list of applications recommended for funding.

7 Approval of the Funding Recommendations

Following programmatic review, the recommended for funding list is reviewed and approved by the Commanding General, USAMRMC, 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 USAMRMC offices and organizations, including CDMRP, USAMRAA, and ORP. During the period of performance for awards (which can vary according to award type and may include extensions), CDMRP actively manages and monitors progress. The awards management process is depicted in **Figure 3**. Over the past 5 years, an average of 839 new awards were made each fiscal year. As of September 30, 2018, CDMRP has managed 16,632 awards throughout its funding history.

Once an application has been recommended and approved for funding, it is assigned a 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 USAMRMC. Technical analysis of the budget with respect to the scope of work to be performed is completed prior to the award being made to maximize savings and avoid overlap in research funding with other funded projects within CDMRP, as well as other federal agencies. 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, with monitoring of the technical progress and research outcomes through annual/quarterly reports, animal and human subjects 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 provides active management in working with the PI and other DOD components to provide oversight, facilitate communication, promote successful completion of awards, and accelerate translation of research outcomes where possible.

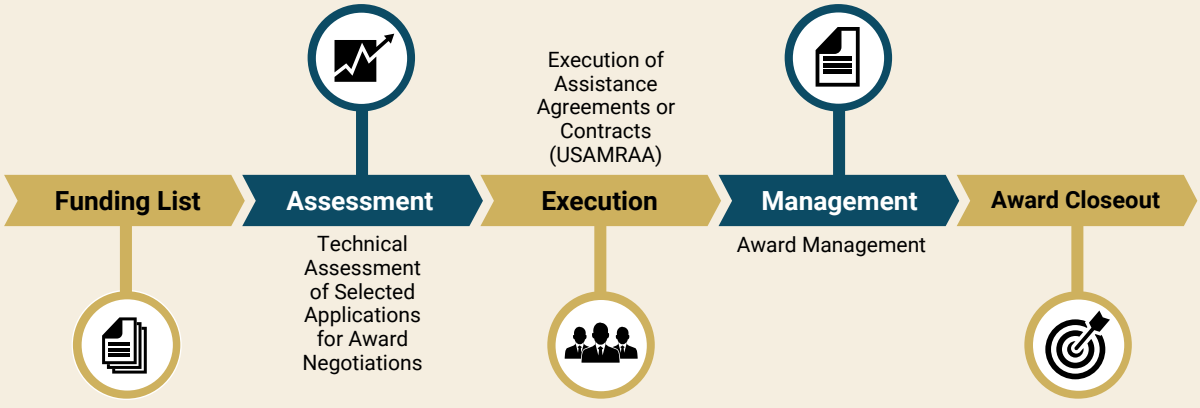


Figure 3. Awards Management Process

9 Award Closeout

Award closeout takes place at both USAMRAA and CDMRP and is usually performed in the 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 (http://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 http://www.dtic.mil/dtic/. Social media outlets used by CDMRP to expand information dissemination strategies include YouTube (http://www.youtube.com/user/CDMRP), Facebook (https://www.facebook.com/TheCDMRP), and Twitter (https://twitter.com/CDMRP); in addition, CDMRP maintains an e-mail listserve of more than 85,000 unique recipients.

MULTISTEP PROCESS TO MINIMIZE AWARD DUPLICATION AND OVERLAP

STEP 1
PIs are required to submit a list of past, current, and pending funding support at the time of application submission.

STEP 2
Screen for duplicate submissions during compliance checks.

STEP 3
Identification of project innovation, research duplication, and overlap during the two-tier review process by peers in the field (specifically program staff from other federal funding agencies).

STEP 4
List of updated funding support at the time of award notification, which is certified by the award recipient's Sponsored Programs Office.

STEP 5
Review of submitted documents and research program sites to assess pending and existing funding support during award negotiations.

STEP 6
PIs are required to provide a list of updated funding support in annual technical progress reports.

STEP 7
Technical review of progress and review of Federal RePORTER annually throughout the award period of performance, which includes a review for funding overlap and duplication.

Vital Partnerships

In FY17, nearly 425 consumers served on CDMRP peer review panels and over 55 served as programmatic reviewers.

Today, over 2,100 consumers have represented their communities and lay organizations at least once since 1992 and their role continues to be vital.

In FY18, nearly 2,690 scientists and clinicians provided necessary subject matter expertise on peer review panels and over 390 scientists and clinicians served as programmatic reviewers. As of September 30, 2018, over 150 scientists, clinicians, and consumers have served as ad hoc programmatic reviewers. Since its inception, approximately 12,012 researchers have been funded by CDMRP to improve the health and quality of life of all people.

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 all have an equal voice and vote in deliberations. 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).

"This experience gave me confidence in the process, knowing how much they truly value the perspective of the patient. They want to hear our voices because our perspective and experience living with MS carry a lot of weight in [the peer review] discussions... I truly believe that through [the MSRP] and other research efforts we will see an end to MS one day."

Emily Reilly
2017 MSRP Consumer Reviewer

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 to translate this knowledge into improved prevention, treatment interventions, patient survival, and quality of life. External experts in the program cycle 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.

MILITARY PARTNERSHIPS

US Army Medical Research and Materiel Command

Vision: Lead the advancement of military medicine

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

CDMRP is located within USAMRMC, the largest medical materiel developer within the DOD, with the responsibility for medical research, development, and acquisition and medical logistics management. USAMRMC is responsible for managing medical research programs that address both military and civilian beneficiaries. The USAMRMC'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. USAMRMC's medical research programs are divided into core and non-core research programs based on their alignment with DOD and Army missions. Core programs are funded through DOD's planning and budget process and align with the principal needs and military operations within the DOD. Non-core programs are funded through congressional line-item additions to the DOD budget. CDMRP provides management support for both types of funding and works in synergy with USAMRMC partners to ensure that its budgetary funds and congressional 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. USAMRMC 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 USAMRMC to remain responsive to the changing needs of the Warfighter. 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 USAMRMC 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 USAMRMC's commitment to remain a good steward of taxpayer dollars and a world-class medical R&D organization.

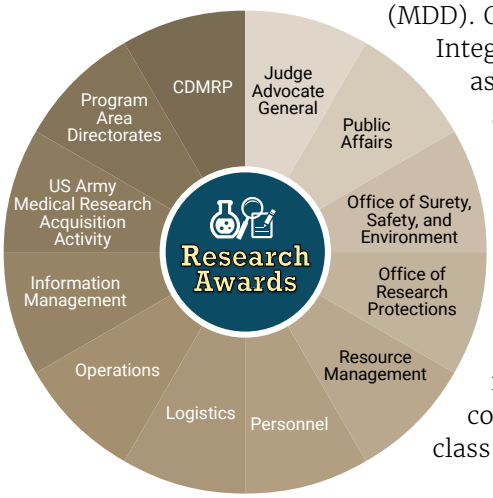


Figure 4. The USAMRMC Team

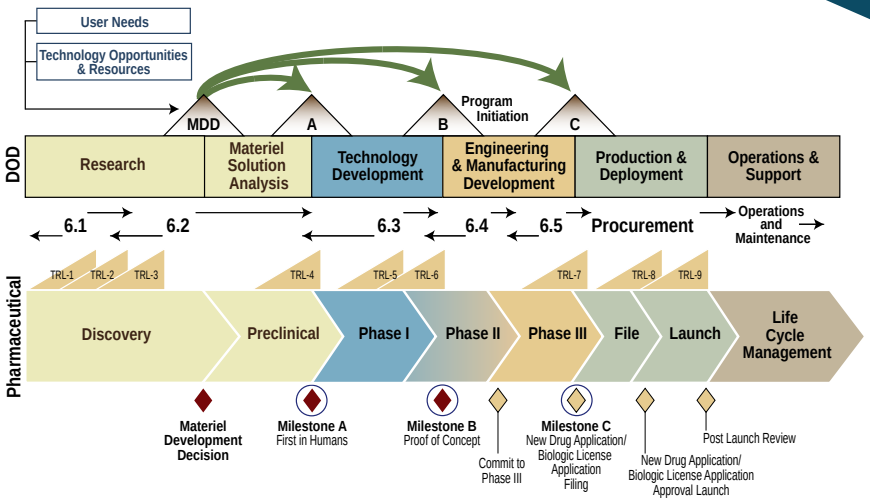


Figure 5. Decision Gate Life Cycle

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 reports to OASD(HA), as shown in **Figure 6**. 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

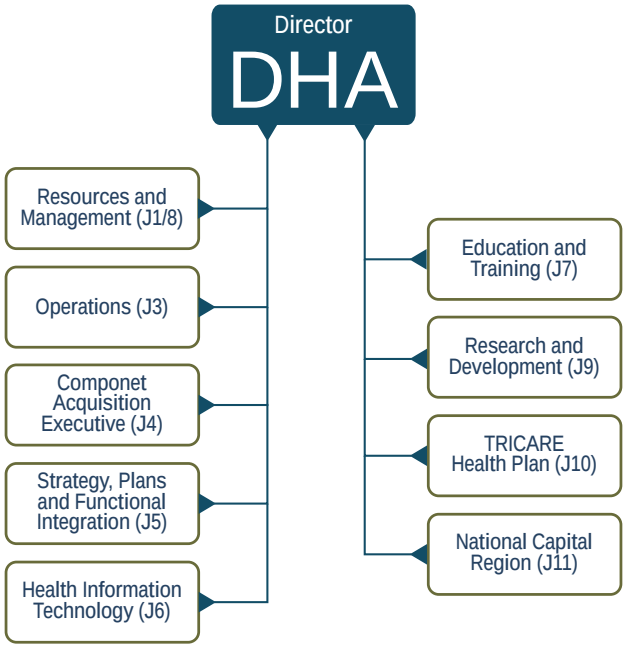


Figure 6. DHA Reporting and Support Structure

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 research and development 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, 17 additional CDMRP-assigned congressional programs presented at R&A meetings in FY17, and these meetings continued into FY18. 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, Research and Development Directorate-funded research. JPCs advise and work through the USAMRMC PADs, which provide strategic oversight of this research. There are currently six active PADs:

- Medical Simulation and Information Sciences Research Program (MSISRP)
- Military Infectious Diseases Research Program (MIDRP)
- Military Operational Medicine Research Program (MOMRP)
- Combat Casualty Care Research Program (CCCRP)
- Radiation Health Effects Research Program (RHERP)
- Clinical and Rehabilitative Medicine Research Program (CRMRP)

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 96-106 in this report). In FY18, 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 the healthcare of Veterans, 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 229 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 48–49 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 $100M 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 19) and the Chronic Effects of Neurotrauma Consortium (CENC; refer to page 18), which are described in further detail on pages 16–30 of this Annual Report.

Additionally, in 2017 and 2018, the VA was invited to have representation on the panel of senior leadership and present VA-funded research efforts during the R&As of CDMRP's programs.

"The DOD funded Dr. Dennis Slamon's early work on Herceptin® and thus benefitted me as an active duty Service member, and now as a Veteran. It is a full circle, with me giving 25 years of service to the DOD, and the DOD giving back to me as a breast cancer patient."

SMSgt (Ret.) Sheila Johnson-Glover

Collaborative Research

Over the years, several programs funded the development of research consortia to build strong partnerships and collaborations in 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 are provided in the following sections.

ALZHEIMER'S DISEASE NEUROIMAGING INITIATIVE

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 [PET] and magnetic resonance imaging [MRI]) and biomarker (cerebrospinal fluid [CSF]) research. Three studies 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):

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.

- Effects of Traumatic Brain Injury and Post-Traumatic Stress Disorder on Alzheimer's Disease in Veterans Using Imaging and Biomarkers in the ADNI (FY11).
- Effects of Traumatic Brain Injury and Post-Traumatic Stress Disorder on Alzheimer's Disease in Veterans with Mild Cognitive Impairment Using the ADNI (FY12).
- Effects of Traumatic Brain Injury and Post-Traumatic Stress Disorder and Alzheimer's Disease on Brain Tau in Vietnam Veterans Using the ADNI (FY13).

ARMED FORCES INSTITUTE OF REGENERATIVE MEDICINE

The Armed Forces Institute of Regenerative Medicine (AFIRM) was established in March 2008 by USAMRMC 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. This interdisciplinary network has been focused on regenerative medicine for the treatment of severely wounded servicemen and women. 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. AFIRM supported nine clinical trials, resulting in the treatment of more than 200 patients with novel therapeutic strategies in wound repair and tissue replacement. In 2013, based on AFIRM's successes, funding for AFIRM II was made available by the same partnership of government agencies. Wake Forest was selected to lead this next phase of AFIRM. AFIRM II includes members from both of the initial AFIRM consortia, along with new investigators. AFIRM II's 60 original research projects span five focus areas that represent critical clinical challenges needing advanced solutions for Wounded Warriors:

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

- Extremity Repair
- Craniomaxillofacial Reconstruction
- Skin Regeneration
- Composite Tissue Allotransplantation and Immunomodulation
- Genitourinary Repair and Lower Abdomen Reconstruction

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. AFIRM 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

The Bridging Advanced Developments for Exceptional Rehabilitation (BADER) Consortium, led by Dr. Steven Stanhope of the University of Delaware, supports the advancement of orthopaedic rehabilitation research capabilities at DOD Military Treatment Facilities (MTFs) and VA sites. Its overarching goal is to partner with MTFs and the Extremity Trauma and Amputation Center of Excellence (EACE) to strengthen and support evidence-based orthopaedic rehabilitation care that results in optimal functional outcomes for Service members with limb loss and limb difference. The BADER Consortium helps strengthen a research-intensive culture at each MTF and works in concert with them to conduct high-impact research studies and help establish self-sustaining research enterprises at these sites, with DOD and VA employees serving as PIs in research projects. BADER Consortium studies have helped change patient care in rehabilitation at many of the facilities, including the prescription of devices for optimal running gait. BADER has funded eight clinical research projects totaling $7.7M and supported 64 projects for the DOD/VA. At this time and as reported by its members, the

The BADER Consortium will improve the quality of life for Warfighters who suffer significant limb injuries in combat through orthopaedic rehabilitation research conducted at several military and civilian research institutions across the country.

Consortium has generated 84 published abstracts and 25 published manuscripts; has obtained grants to fund an additional 16 projects totaling over $13M and awaits decision on 10 pending applications.

BADER Consortium-funded projects include:

- A Virtual Reality-Based Training Intervention to Reduce Falls in Patients with Lower-Limb Amputations.
- Walk-to-Run Training Using Real-Time Kinetic Feedback to Improve Amputee Running.
- A Qualitative Study of Patient-Reported Outcomes in People with Major Limb Trauma to Measure Their Level of Recovery.
- Identifying the Enhanced Gait Function Benefits From Using a Powered BionX Medical Technologies (BiOM) Ankle Prosthesis for Lower-Limb Amputees.
- A Science-Based Method for Prescribing Running-Specific Leg Prosthesis to Optimize Running Performance.
- Assessing Rehabilitation Outcomes in the Clinical Environment to Support Evidence-Based Practice in MTFs.
- Studying Community Reintegration, Functional Outcomes, and Quality of Life After a Major Extremity Trauma to Enhance Patient Care and Future Health Studies.
- Criteria to Identify Prosthetic Foot Characteristics That Best Support Physically Demanding Tasks.

THE CHRONIC EFFECTS OF NEUROTRAUMA CONSORTIUM

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, diagnosis, and treatment/rehabilitation of mTBI to neurodegeneration. CENC is led by PI Dr. David Cifu at Virginia Commonwealth University, with the assistance of two Co-PIs: COL Sid Hinds at USAMRMC and Dr. Rick Williams at Research Triangle Institute (RTI) International. Currently, CENC 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 (OIF), Operation Enduring Freedom (OEF), and Operation New Dawn (OND) conflicts. Another study expanded upon DOD funded studies in Service member populations in theater, was completed under CENC sponsorship and is continuing under NIH funding. 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://cenc.rti.org/.

The consortium's efforts will address the common co-morbidities associated with chronic mTBI, such as neurosensory system involvement (vision, balance, hearing, pain) and psychological dysfunction.

CONCUSSION ASSESSMENT, RESEARCH, AND EDUCATION CONSORTIUM

The National Collegiate Athletic Association (NCAA)-DOD Grand Alliance Concussion Assessment, Research, and Education (CARE) Consortium is a joint DOD and NCAA 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. Since its inception in 2014, the 4-year consortium project has enrolled 39,605 student athletes and service academy cadets at 30 performance sites (26 NCAA universities and 4 Service academies). The consortium is comprised of three arms. The Administrative and Operation Core, the first arm, is directed by Dr. Tom McAllister at Indiana University and provides oversight, management, and support to the Consortium. The second arm is the Longitudinal Clinical Study Core (CSC), directed by Dr. Steve Broglio at the University of Michigan. The CSC 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. As of March 2018, the study team has captured 2,869 concussions from the student athletes and service cadets enrolled, one-third of which were captured at the service academies. The third arm is the Advanced Research Core (ARC), directed by Dr. Mike McCrea at the Medical College of Wisconsin. The ARC builds upon the work being performed by the CSC, allowing for more advanced research projects, such

as testing impact sensor technologies, studying potential biomarkers, and evaluating concussion with advanced neuroimaging. The ARC has six performance sites, including four NCAA universities and two service academies. As of March 2018, 2,278 athletes and service cadets have been enrolled, and 347 concussions have been captured; over half of the concussions studies were athletes and cadets at the service academies. 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 continually submitted to the Federal Interagency Traumatic Brain Injury Research (FITBIR) informatics system and will be released to the public at project completion. The NCAA recently released new guidelines regarding football practice as well as guidance for diagnosis and management of concussion, based in part on the findings from the CARE Consortium. The studies performed by the consortium have been presented in several forums, and initial results from the study were published in March 2017 in the *American Journal of Sports Medicine*. Data from the CARE Consortium has since been included in several additional publications. The full research articles and more information can be found at http://careconsortium.net/.

THE CONSORTIUM TO ALLEVIATE POST-TRAUMATIC STRESS DISORDER

CAP is a cutting-edge, joint VA and DOD effort to understand and treat PTSD and related conditions in active duty military Service members and Veterans. 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 and in the final data analyses phases. Numerous VA, academic, and military institutions across the United States participate in CAP. Additional information can be found at https://tango.uthscsa.edu/consortiumtoalleviateptsd/.

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.

DETECTION OF EARLY LUNG CANCER AMONG MILITARY PERSONNEL CONSORTIUM

The Detection of Early Lung Cancer Among Military Personnel (DECAMP) Consortium is led by Dr. Avrum Spira 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. The consortium 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 (CT) 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.

GULF WAR ILLNESS CONSORTIUM

The GWI Consortium is led by Dr. Kimberly Sullivan of Boston University and brings 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.

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.

INSTITUTE FOR TRANSLATIONAL NEUROSCIENCE

The Institute for Translational Neuroscience (ITN), a consortium comprised of 22 institutions, 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 sixth year of operation, 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.

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

To facilitate the transition from bench to bedside, a Translational Coordinating Core was established 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)

The Major Extremity Trauma Research Consortium (METRC) was initially established in September 2009 with funding from the DOD and the Orthopaedic Extremity Trauma Research Program (OETRP at USAISR). The consortium would later be expanded in both size and scope one year later through a cooperative agreement with the DOD's Peer Reviewed Orthopaedic Research Program (PRORP) under which METRC2 was funded. CDMRP assumed management of the METRC2 studies in 2015. METRC3 was selected for funding via the competitive FY15 PRORP Orthopaedic Care and Rehabilitation Consortium Award (OCRCA) PA. The OCRCA leveraged METRC infrastructure to initiate additional studies that are funded under METRC3. With the FY15 award, the METRC's historically acute care focus shifted to incorporate several rehabilitation focus areas, leading to the newly titled Major Extremity Trauma and Rehabilitation Consortium (METRC). The coordinating center for METRC 1, 2, and 3 studies is located at the Johns Hopkins Bloomberg School of Public Health. This center collaborates with 4 MTFs, 22 core civilian trauma centers, and 32 satellite centers to conduct 14 total studies under the METRC core umbrella. A number of other studies associated with METRC core studies are also being conducted. Most recently, the METRC team received additional funding through an FY16 Joint Warfighter Medical Research Program (JWMRP) award. Funding form this award will support the continuation of two ongoing METRC2 clinical studies as well as an integration of METRC Clinical Practice Guidelines (CPGs) and Appropriate Use Criteria (AUC).

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.

Led by Dr. Ellen MacKenzie of Johns Hopkins University and Dr. Michael Bosse at Carolinas Medical Center, the core METRC2 studies include:

- Comparing Patient Outcomes Post Limb Salvage and Amputation Among Patients With Severe Foot and Ankle Trauma
- Comparing Outcomes in Patients Undergoing Transtibial Amputation With or Without Tibia-Fibula Synostosis
- Developing a Novel Tool to Aid Clinicians in Timely and Accurate Diagnoses of Acute Compartment Syndrome
- Evaluating Multimodal Approaches for Peri-Operative Pain Management in Treatment of Lower Limb Fractures
- Implementing a Collaborative Care Intervention to Address Patients' Psychosocial Needs and Improve Health-Related Quality of Life

Core METRC3 studies include:

- Measuring Patient-Specific Injury and Progression of Immunologic Response to Optimize Orthopaedic Interventions in Multiply Injured Patients
- Improving Pain and Function Following Orthopaedic Trauma: A Cognitive-Behavioral Based Physical Therapy Approach
- Early Advanced Weight Bearing for Periarticular Knee and Pilon Injuries: An RCT Using the Antigravity Treadmill
- Early Mechanical Stabilization of Bleeding in Disruption of the Pelvic Ring: A Multicenter, Prospective Observational Study
- Long-Term Consequences of Major Extremity Trauma: A Pilot Study

More information regarding these studies and their results can be found at http://metrc.org.

MILITARY SUICIDE RESEARCH CONSORTIUM

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

In its initial funding period, 25 studies and multiple Postdoctoral Pilot Projects and Dissertation Completion Awards were funded. These studies were conducted at numerous VA and military installations across the country and covered a broad spectrum of the research continuum, ranging from etiological to prevention/screening and treatment. Populations studied included Service members, Veterans, beneficiaries, and civilians. In FY16, five years of additional DOD funding was obtained by the MSRC 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. Thirteen new studies have been funded since FY16 and additional studies will be funded over the next year.

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, a plan developed by multiple federal agencies in response to an Executive Order issued by the President, as playing a role in achieving the vision for suicide prevention research.

Twenty-four of the funded studies are now complete and have yielded important results. For more information related to the funded studies, please visit https://msrc.fsu.edu/funded-research.

This USAMRMC 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.

NEUROFIBROMATOSIS CLINICAL TRIALS CONSORTIUM

The Neurofibromatosis Clinical Trials Consortium (NFCTC) was established by the DOD Neurofibromatosis Research Program (NFRP) in 2006 to develop and perform clinical trials for the treatment of neurofibromatosis (NF) complications in children and adults. The NFCTC was first funded to initiate clinical trials in 2006 and subsequently in 2011 and 2016. This includes the development of clinical trials for the treatment of NF complications, including plexiform neurofibromas, cognitive disorders, low-grade gliomas, vestibular schwannomas, schwannomatosis, tibial pseudarthrosis, and malignant peripheral nerve sheath tumors.

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 again in FY16.

The consortium is composed of an Operations Center based at the University of Alabama at Birmingham, 15 clinical sites and 9 collaborating sites. While the Operations Center provides administrative, data management, and statistical support to the NFCTC, each of the clinical and collaborating sites has 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, the group has rapidly moved promising therapeutics for NF into clinical trials. Information on the clinical trials and resulting publications can be found at http://www.uab.edu/nfconsortium and at http://cdmrp.army.mil/nfrp/consortium/nfrpctc.

OVARIAN CANCER ACADEMY

Since FY09, the Ovarian Cancer Academy (OCA) has brought together talented and highly committed Early Career Investigators (ECIs) with their mentors and Academy Leadership to fulfill the Ovarian Cancer Research Program's (OCRP) vision of a unique, virtual OCA that supports the development of career ovarian cancer researchers. 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, two new FY17 ECI-mentor pairs were welcomed into the OCA, which currently brings the numbers of OCA ECIs (FY12-FY17) to 13. All 7 of the original FY09 ECIs successfully completed their awards, contributing 260 publications, 129 presentations, and 63 grants worth $17.1M. To date, the OCA ECIs have demonstrated remarkable progress, resulting in 372 publications and 227 abstracts focused on ovarian and other gynecologic cancers. Their growth as independent, committed ovarian cancer researchers is evident in their 105 funded (non-OCA) grants 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 Pittsburgh in October 2017 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 career mapping and mentorship, and a mock study panel discussion. The ECIs also had the opportunity for professional networking with a team from the Magee-Women's Research Institute of Pittsburgh, who presented an overview of their Regional Ovarian Cancer Research Facilities. OCA members also participated in the American Association for Cancer Research's (AACR's) subsequent Advances in Ovarian Cancer Research Special Conference, which included a platform presentation from an OCA alum and posters highlighting ECI research. The 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.

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

OVARIAN CANCER CONSORTIUM

Early ovarian cancer usually has no obvious symptoms, and currently there is no sufficiently accurate screening test for the early detection of ovarian cancer in average-risk women. The National Cancer Institutes (NCIs) Surveillance, Epidemiology, and End Results (SEER) Program estimates diagnosis of 22,240 new cases and 14,070 deaths due to ovarian cancer in 2018. The majority of cases are diagnosed at later stages, and the 5-year relative survival rate for cases where the cancer has metastasized is 29.2% (United States, SEER 2008-2014). A multi-institutional team originally headed by Dr. Robert Kurman and now led 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, successfully competed for the first Ovarian Cancer Consortium Award (OCCA) offered in FY10. Their objective is to develop a prevention strategy to reduce the burden of ovarian cancer, and toward this end, they are focused on definitively identifying and characterizing early changes associated with the disease. To accomplish this, the OCCA tested the hypothesis that an early lesion in the fallopian tube, called a serous tubal intraepithelial carcinoma (STIC), is the precursor of ovarian high-grade serous carcinomas (HGSC), which account for a majority of ovarian cancers and ovarian cancer-related mortalities. The consortium's research plan has four preclinical projects focused on the molecular and morphological characterization of the precursor lesions/STICs as well as a fifth epidemiological study designed to evaluate whether these STIC characteristics are modifiable by oral contraceptives or anti-inflammatory agents.

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

The Ovarian Cancer Consortium has completed a substantial body of work which involved evaluating STICs as precursor lesions of HGSCs, identifying the early molecular changes that precede the development of STICs, introducing the role of the epigenetic modulator Ten-Eleven Translocation protein 1 (TET1), exploring the chemopreventative efficacy of a combination statin and nonsteroidal anti-inflammatory drug (NSAID) regimen,

and identify that differential gene expression exists between patients with ovarian cancer with a BRCA1 (breast cancer 1) mutation status and a non-mutated status thus highlighting multiple potential therapeutic targets for disease control.

The more recent accomplishments of the consortium include findings which support:

- A role for several genes involved in metabolism and glutathione-mediated oxygen and xenobiotic antioxidant response which were up-regulated in fimbrial epithelial cells compared to the ampulla. This data provides insight into disease susceptibility as fimbrial epithelial cells express a cadre of genes to protect their genome from cytotoxic stressors found it the microenvironment and follicular fluid released from the ovary.
- Loss of the CCAAT/enhancer-binding protein delta (CEBPD) as an early step in serous ovarian carcinogenesis and a role for it in promoting a partial mesenchymal to epithelial transition (MET). This suggests CEBPD may be a potential target for the regulation of epithelial to mesenchymal transition (EMT) or MET in the development of HGSC.
- A role for leukocytes in the progression or inhibition of early disease, as indicated by a significant difference in their percentages within STIC lesions and HGSC cases compared to normal cases. These results were independent of the ovarian cycle with no inherent difference in proliferation rates between normal and BRCA1/2 mutation carriers at the distal fallopian tube epithelium (FTE). However, they did find a proliferative difference present at later stages of disease progression when an early lesion is identifiable, suggesting that molecular changes to the FTE occur later in the development of the disease.
- Correlation of a deregulated retinoblastoma (Rb1) pathway with clinical outcomes. Their data substantiates the role of defective Rb1 in early serous tumor development and as a target for chemotherapeutic and novel therapeutic strategies.

OVARIAN CANCER OUTCOMES CONSORTIA

In FY12, OCRP offered the Outcomes Consortium Development Award to lay the groundwork needed to build a multi-institutional research effort that could specifically identify and understand predictors of disease outcomes in patients with ovarian cancer. The intention was to bring together teams of talented researchers to focus on discovering what distinguishes the small subset of patients with ovarian cancer who become long-term survivors (≥ 10-year survival from diagnosis) from other ovarian cancer survivors. In FY15, OCRP offered the Outcomes Consortium Award to move the consortia from the development phase to the research phase, where each consortia would use its own set of resources and focus areas in an effort to identify predictors of long-term survival to enable tailored therapies that maximize patient survival and quality of life.

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.

Two teams, one led by Dr. Malcom Pike and the other by Dr. Michael Birrer, were chosen for the FY15 Outcomes Consortium Award. The Multidisciplinary Ovarian Cancer Outcomes Group (MOCOG), led by Dr. Pike at Memorial Sloan Kettering Cancer Center, 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. The MOCOG is an international collaboration of 10 sites that will leverage samples, data, and techniques to search out novel immune therapy approaches to ovarian cancer treatment and the patients who would benefit from these targeted immune therapies. The Ovarian Cancer Consortium for the Genomic, Epigenetic, and Quality of Life Characteristics of Long-Term Survival, led by Dr. Birrer at the University of Alabama at Birmingham, 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.

Dr. Birrer's group utilized data obtained from a longitudinal analysis of quality of life obtained from patients participating in Gynecologic Oncology Group trial-172 (GOG-172), a clinical trial testing intraperitoneal and intravenous chemotherapy, to develop a descriptive profile for short (STS), intermediate, and long-term survivors (LTS). Initial analysis indicates LTS 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 STS and intermediate-term survivors. They posit that this initial analysis supports the case for quality of life as an independent and significant predictor for long-term survival and may be useful as a stratification

factor in clinical trials or in counseling patients as they examine treatment options. The team also initiated genomics and immunohistochemistry (IHC) analysis of tumor samples diagnosed with early stage ovarian cancer in order to identify a signature for recurrence of early stage tumors. Patient advocates from 10 advocacy organizations participate as partners in the Consortium.

Dr. Pike's group completed the exhaustive task of confirming their 1,506 LTS, moderate (5–7 years) survivors, and STS samples as HGSC as well as matching the LTS samples with an equal number of moderate survivors and STS based on study population, year of diagnosis, and age at diagnosis. They are currently collecting dietary and behavioral data for all survivors and performing whole-genome analysis of subsets of LTS and STS patients. This team demonstrated and published an article entitled, "Homologous Recombination DNA Repair Pathway Disruption and Retinoblastoma Protein Loss Are Associated with Exceptional Survival in High-Grade Serous Ovarian Cancer." Another publication reported that CD8 tumor infiltrating lymphocytes (TILs) densities were higher in tumors from patients who experienced exceptional progression-free and overall survival but not in patients who demonstrated multiple responses to chemotherapy. Members of the team presented their findings at 10 conferences. Dr. Pike's team includes ovarian cancer survivors who have been integral in project design, dissemination of findings, and engaging with advocacy groups.

PAIN MANAGEMENT COLLABORATORY

Started in FY17, the Pain Management Collaboratory (PMC) Program is an interagency partnership between NIH, the DOD, and the VA. This partnership is 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.

CDMRP is managing the four projects being funded by the DOD:

- Testing Two, Scalable, Veteran-Centric Mindfullness Based Interventions for Chronic Musculoskeletal Pain: A Pragmatic Multisite Trial, led by Dr. Diana Burgess at the Minneapolis VA Health Care System
- Resolving the Burden of Low Back Pain in Military Service Members and Veterans: A Multi-Site Pragmatic Clinical Trial (RESOLVE Trial), led by Dr. Shawn Farrokhi at the Naval Medical Center, San Diego
- Targeting Chronic Pain in Primary Care Settings Using Internal Behavioral Health Consultants, led by Dr. Donald McGeary at the University of Texas Health Science Center at San Antonio
- Ultrasound Guided Percutaneous Peripheral Nerve Stimulation: A Non-Pharmacological Alternative for the Treatment of Postoperative Pain, led by Dr. Brian Ilfield at the University of California, San Diego

These projects 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/meditative interventions, movement interventions (e.g., structured exercise, tai chi, yoga), manual therapies (e.g., spinal manipulation, massage, acupuncture), psychological and behavioral interventions (e.g., cognitive behavioral therapy), integrative approaches that involve more than one intervention, and integrated models of multi-modal care.

PHARMACOTHERAPIES FOR ALCOHOL AND SUBSTANCE ABUSE CONSORTIUM

On September 30, 2015, RTI was awarded a $10.8M, 5-year award from the Alcohol and Substance Abuse Disorders Research Program (ASADRP) to establish the Pharmacotherapies for Alcohol and Substance Abuse (PASA) Consortium. The Consortium is led by Dr. Rick Williams from RTI, in collaboration with Baylor College of Medicine and the Uniformed Services University of the Health Sciences (USU). The PASA Consortium 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. The three broad aims are: (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. Four

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

studies were funded (two pre-clinical and two clinical), covering topics that assessed the effectiveness of pharmacotherapies on alleviating PTSD and Alcohol Use Disorder (AUD). A second Request for Applications was recently released, and a planning grant was awarded to examine the role of kappa opioid receptor antagonists for the treatment of AUD and comorbid PTSD.

PROSTATE CANCER BIOREPOSITORY NETWORK

The Prostate Cancer Biorepository Network (PCBN) is a bioresource that provides prostate cancer tissue and other patient samples to prostate cancer investigators worldwide. The Prostate Cancer Biorepository Resource Network Award was first offered in FY09, with the intention of providing infrastructure support for the development of the PCBN – envisioned as a biorepository with high-quality, well-annotated specimens obtained in a systematic, reproducible fashion using optimized and standardized protocols. That award funded two sites, Johns Hopkins University and New York University, and they developed a shared infrastructure, including establishment of a website; optimized processes for specimen collection, processing, and annotation; informatics and data management; intellectual property, legal/ethical/regulatory issues; and policies for specimen distribution.

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

The network was expanded in FY13 to further enrich the PCBN with a larger spectrum of prostate cancer biospecimens, with particular emphasis on acquiring and distributing rare samples. The combined resources of the five Prostate Cancer Research Program (PCRP)-funded sites – Johns Hopkins University, New York University, the University of Washington, Memorial Sloan Kettering Cancer Center, and Washington University in St. Louis – further enhanced the development of this resource. 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 (PDX) models. The PCBN derives its specimen resources from extensive, well-characterized patient populations with a long history of supporting clinical and biomarker research. All specimens in the PCBN contain standard pathology data, and the majority of specimens are linked to clinical and outcome data. Some also have epidemiologic data, and all are supported by an informatics infrastructure.

The types of specimens that are available include tissue microarrays, fresh frozen and paraffin-embedded tissue, body fluids, and derived DNA, RNA, and protein. They have distributed more than 3,000 patient samples. As a resource for the prostate cancer research community, PCBN biospecimen usage has resulted in 39 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*. Continued success and utilization of the PCBN led the PCRP to openly compete for continued financial support of a publically available prostate cancer biorepository for use by the research community. Starting in October 2018, the PCBN will be providing biospecimens available from Institute for Cancer Research, Johns Hopkins University, New York University, the University of Washington, and Washington University in St. Louis, maintaining the PCBN's status as the largest, most comprehensive prostate cancer biorepository in the world (for additional information, see http://prostatebiorepository.org/).

PROSTATE CANCER CLINICAL TRIALS CONSORTIUM

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 22 participating affiliate sites. The goal was to combine the work of leading investigators with the unique institutional resources of outstanding clinical research sites across the United States 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,

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.

with three agents having now received approval by the FDA: (1) abiraterone acetate, which blocks formation of testosterone by inhibiting CYP17A1 (Cytochrome P450 17A1); (2) enzalutamide, which binds to the ligand-binding domain of the androgen receptor (AR), prevents nuclear translocation, and blocks AR interaction with coactivator proteins, thereby preventing transcription of AR-regulated genes; and (3) apalutamide, the first AR antagonist to be approved for use by patients with non-metastatic castration-resistant prostate cancer.

The consortium's successful acceleration and streamlining of the clinical trial process can be attributed to its unique infrastructure, which addresses the scientific, legal, regulatory, database, budgetary, and management concerns of its members. The PCCTC has approved 214 clinical trials for activation, 160 of which have been completed (closed to accrual), with an additional 54 trials either active or pending activation. More than 7,432 patients have been enrolled in these trials, 12% representing patients from disproportionately affected populations. The consortium is also at the forefront of the personalized medicine arena, incorporating liquid biopsies to identify distinct prostate cancer subtypes for which specific drugs are available and to monitor how an individual's cancer changes biologically in response to particular treatments. 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/).

SOUTH TEXAS RESEARCH ORGANIZATIONAL NETWORK GUIDING STUDIES ON TRAUMA AND RESILIENCE

The South Texas Research Organizational Network Guiding Studies on Trauma and Resilience (STRONG STAR) is a multidisciplinary and multi-institutional research consortium funded by the DOD. STRONG STAR is dedicated to the development and evaluation of the most effective interventions for the detection, prevention, and treatment for combat-related PTSD. The STRONG STAR team of more than 150 military, civilian, and VA investigators and clinicians is centered at the University of Texas Health Science Center, San Antonio, and also embedded within nearby Fort Hood, where they coordinate recruitment of human subjects with other military and Veteran locations for collaborating investigators from across the country. The STRONG STAR Consortium has completed 14 projects, including retrospective data analyses, epidemiological studies, and 8 clinical studies. The results of the most of completed studies have been published. Final results of the clinical trials conducted by STRONG STAR, several of which are highly anticipated as the first testing of evidenced-based treatments for PTSD in military populations, are available (https://tango.uthscsa.edu/strongstar/scipubs.asp). In addition to the STRONG STAR studies funded under the PTSD Multidisciplinary Research Consortium Award mechanism, the consortium has partnered with nationwide investigators and institutions of higher education to secure approximately $50M in additional peer-reviewed funding from the DOD, VA, NIH, and private foundations to support over 20 additional STRONG STAR-affiliated projects.

The goal of the STRONG STAR Consortium is to reduce or eliminate combat-related PTSD in active duty military and recently discharged Veterans.

SURGICAL TIMING AND REHABILITATION CONSORTIUM

The Surgical Timing and Rehabilitation (STaR) Consortium, led by Dr. James Irrgang of the University of Pittsburgh, is a multi-site clinical trial 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 (ACL) reconstruction surgery; however, there is little evidence to support this practice. The consortium is comprised of two separate studies that will determine the most optimal times for surgery and post-operative rehabilitation to increase the rate of return for individuals with MLKIs to their preinjury physical function and level of activity. The first aim is to determine the combined effects of early versus delayed timing of surgery and rehabilitation on the time it takes an individual to return to their pre-injury status and activity. The second aim is to investigate the effects of early versus delayed rehabilitation. This second aim will include participants with MLKIs, for which the timing of surgery cannot be randomized for any number of reasons. In order to provide the support structure and scientific evidence needed to address the scientific question, the University of Pittsburgh has

brought together a robust governance structure and highly accomplished research study team. Research participants will be recruited at a total of 25 clinical sites comprised of 5 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.

TEAM APPROACH TO THE PREVENTION AND TREATMENT OF POST-TRAUMATIC EPILEPSY

The goal of the Team Approach to the Prevention and Treatment of Post-Traumatic Epilepsy (TAPTE) is to establish a multi-center, multi-investigator research team focused on post-traumatic epilepsy (PTE). 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 Citizens United for Research in Epilepsy (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 USAMRMC, who proactively monitor research progress and advise the consortium on which directions to take to ensure ultimate success. Research was recently initiated, and the lead investigators continue to build their research partnerships.

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

TRAUMATIC BRAIN INJURY ENDPOINTS DEVELOPMENT INITIATIVE

With support of a $17M, 5-year award from the DOD, and direct collaboration with the FDA, 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 for which there are currently no FDA-approved diagnostics or therapeutics. These endpoints include clinical outcome assessments (COAs), blood-based biomarkers, and neuroimaging biomarkers. The TED team is led by PI Dr. Geoff Manley at the University of California, San Francisco. Stage I of the TED award has been focused on establishing a TED database consisting of integrated clinical outcomes, imaging, proteomic, and genomic data from ongoing and legacy TBI studies across civilian, military, and sports cohorts. Stage II allows for large-scale validation studies of candidate clinical outcome assessments and biomarkers selected in Stage I, leveraging the existing research infrastructure and clinical study networks of the Transforming Research and Clinical Knowledge in TBI (TRACK-TBI), the Concussion Research Consortium (CRC), and CENC. Four seed projects were initiated under Stage I, and a fifth project was initiated under Stage II:

- Project 1: An Evidence-Based Clinical Outcome Assessment Platform (EB-COP) to Advance the Identification and Validation of COAs for use as FDA-Qualified Drug Development Tools
- Project 2: Development and Validation of a Cognition Endpoint for Traumatic Brain Injury Clinical Trials
- Project 3: Enhancing the "Regulatory Readiness" of Top TBI Biomarkers Toward FDA Drug Development "Biomarker Qualification Program" Submission
- Project 4: CT and MRI Prognostic Biomarkers for Mild to Moderate Traumatic Brain Injury
- Project 5: The TED Friends Control Study Leveraging the Infrastructure of the Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK-TBI) Network

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.

In addition, the TED initiative has received letters of support and recognition from the FDA in support of the initiative's efforts related to specific TBI-related outcomes. More information about the TED initiative can be found at https://tbiendpoints.ucsf.edu/.

UNDERSTANDING GULF WAR ILLNESS: AN INTEGRATIVE MODELING APPROACH

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 Nova Southeastern University, 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 (TNF) 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. Results of this pilot study will be used to inform interventions under a newly established FY17 Clinical Consortium awarded to Dr. Nancy Klimas. In addition to building on the achievements of the integrative modeling approach, the new clinical consortium is expected to conduct collaborative clinical trials, through Phase II, for the management of GWI treatment. Additional research outcomes from the initial consortium include examination of the physiological effects of Gulf War–era chemical exposure and exercise stress in GWI animal models, with a focus on cardiac, autonomic, and body compositions parameters. Results to date suggest there are cardiac changes associated with Gulf War–era exposure.

PARTICIPATION IN OTHER FEDERAL AND NON-FEDERAL ORGANIZATION EFFORTS

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

ADVISORY COMMITTEE ON BREAST CANCER IN YOUNG WOMEN

A Centers for Disease Control and Prevention (CDC)–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.

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.

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.

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 IACC 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 (ILAE) TASK FORCE

The overall goal of this new group will be to examine this topic and recommend how the ILAE 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 (NAPA)

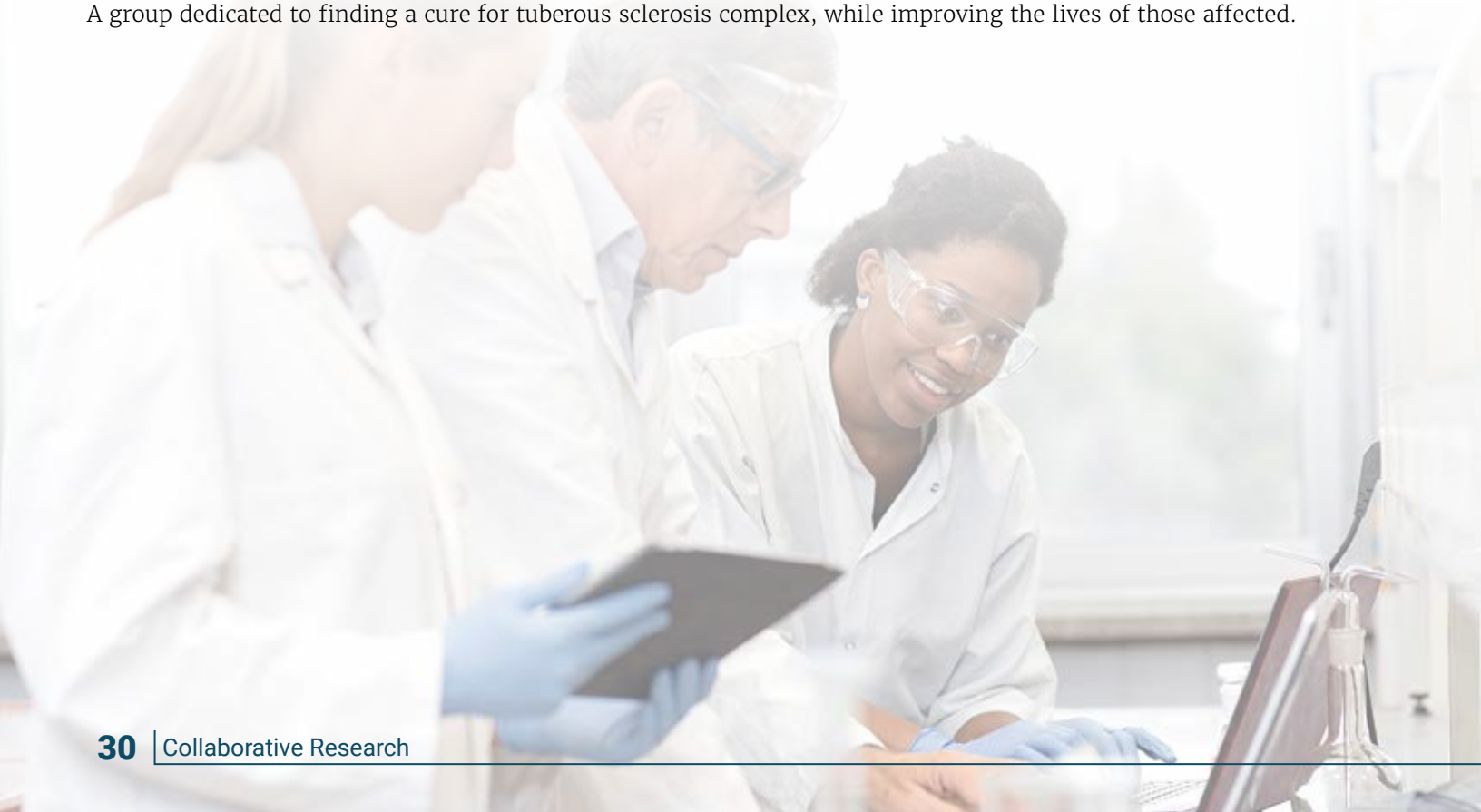
A group that combines federal efforts to coordinate AD and related dementia (ADRD) research. The National Plan for AD/ADRD is updated annually from this interagency collaboration in conjunction with the public-private Advisory Council on Alzheimer's Research, Care, and Services.

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.



Our Programs

The 30 research programs highlighted in this section share many common features, yet each program is unique and emphasizes the specific needs of the research and advocacy communities. These programs are detailed on the following pages.

Alcohol and Substance Abuse Disorders Research Program

VISION

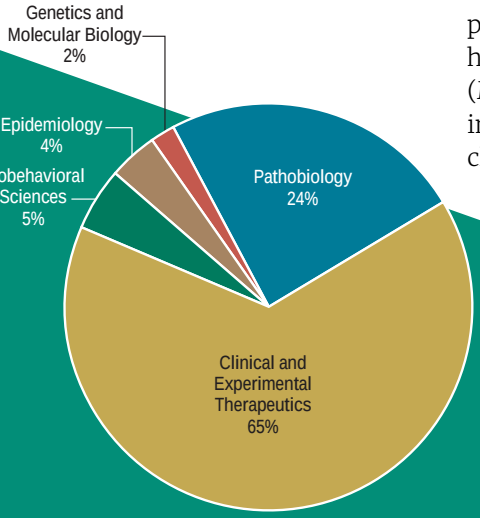
Decrease the clinical impact of alcohol and substance abuse.

MISSION

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

PROGRAM HISTORY

The 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 ASUD, 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. The 2013 IOM report, "Substance Use Disorders in the U.S. Armed Forces," characterized the overall prevalence of heavy drinking at 20% and the overall prevalence of illicit drug use at 12%, and 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. Substance abuse was involved in 30% of the Army's suicide deaths from 2005-2009 (National Institute on Drug Abuse, 2011). 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 (McCarthy and Petrakis, 2010). If successful, this approach could result in translation of contemporary basic science knowledge into enhanced clinical pharmacological treatment protocols for ASUDs.



FY10-FY17 ASADRP Portfolio Investment by SCS Code

INSTITUTE OF TRANSLATIONAL NEUROSCIENCE CONSORTIUM

DEVELOPMENT OF AN ANIMAL MODEL AND NOVEL TREATMENTS FOR COMORBID POST-TRAUMATIC STRESS DISORDER AND COCAINE ADDICTION

Lori A. Knackstedt, PhD, University of Florida

Dr. Knackstedt's team developed a novel animal model of comorbid PTSD and cocaine addiction in order to screen medications for their ability to reduce cocaine relapse. Following a brief exposure to a stressor, rats characterized as displaying long-lasting PTSD-like anxiety display greater levels of persistent cocaine-seeking than do stressed rats that are "resilient" to the stressor. The antibiotic ceftriaxone prevented cocaine relapse in non-stressed controls and resilient rats while having only a modest effect in PTSD-like rats. Combination therapy with ceftriaxone and a positive allosteric modulator of the mGlu5 receptor was able to fully prevent cocaine relapse in PTSD-like rats, while also reducing signs of anxiety.

N-ACETYLCYSTEINE TREATMENT OF HAZARDOUS OR HARMFUL ALCOHOL USE IN VETERANS WITH TBI

Steven L. Batki, MD, Northern California Institute for Research & Education and UCSF School of Medicine, San Francisco Veterans Health Care System

Dr. Batki's clinical research aims to improve the treatment of AUD in Veterans with the complex co-occurring disorders of TBI and PTSD. Veterans with this form of polytrauma have high rates of alcohol misuse and are especially vulnerability to the harmful effects of alcohol, yet there have been few efforts to design treatments that address their multiple problems. Dr. Batki is conducting clinical trials of medications such as N-acetylcysteine (NAC), an over-the-counter nutritional supplement with very few side effects, to treat Veterans with TBI and AUD. Findings from his current work, a pilot controlled clinical trial of NAC, suggests that NAC may help reduce alcohol use, PTSD symptoms, and impulsivity in Veterans with TBI, and may therefore improve the care of these patients.

THE PHARMACOTHERAPIES FOR ALCOHOL AND SUBSTANCE ABUSE CONSORTIUM

ASSESSING PHARMACOTHERAPIES IN ANIMAL MODELS OF POST-TRAUMATIC STRESS DISORDER AND ALCOHOL USE DISORDER

Colin N. Haile, MD, PhD, University of Houston

Dr. Haile's work focuses on assessing promising medications in animal models of PTSD and AUD to determine if they have potential therapeutic use for humans who suffer from these disorders. Dr. Haile's preclinical trial is testing the ability of medications (a kappa opioid antagonist, doxazosin, a GABA-B positive allosteric modulator, and baclofen) to reduce behavioral signs of PTSD and AUD in these animal models to assess the mechanism of action and as proof of concept enabling studies for FDA approval of human Phase II clinical trials.

ZONISAMIDE AS A NEW TREATMENT FOR PTSD & CO-OCCURRING AUD

Christopher Verrico, PhD, Baylor College of Medicine

Dr. Verrico's two current studies focus on treating PTSD and AUD concurrently to facilitate improvements in PTSD symptoms and reductions in alcohol use. The Alcohol Interaction Study (co-PI, Dr. Dewleen Baker), a human laboratory study on 10 subjects, is intended to provide safety data needed for additional study of a novel, selective glucocorticoid antagonist. The objective of the zonisamide study is to determine if, compared to placebo, zonisamide is a safe and efficacious treatment for PTSD and AUD in Veterans with PTSD and co-occurring AUD. This trial is a randomized, double-blind study of 5 weeks of treatment with zonisamide in 60 veterans.

Amyotrophic Lateral Sclerosis Research Program

VISION
Improve treatment and find a cure for ALS.

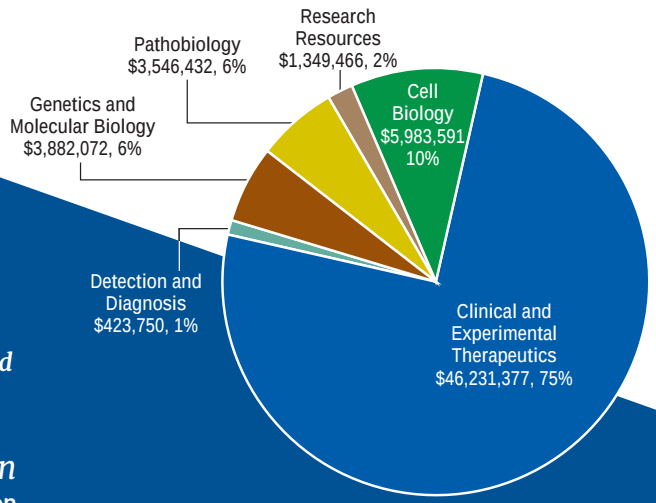
MISSION
Fund innovative pre-clinical research to develop new treatments for ALS for the benefit of Service members, Veterans, and the general public.

PROGRAM HISTORY
Amyotrophic Lateral Sclerosis (ALS), also known as "Lou Gehrig's disease," is an incurable, degenerative neurological disorder. The Amyotrophic Lateral Sclerosis Research Program (ALSRP) is guided by a vision to improve treatment and find a cure for ALS. The ALSRP was created in FY07 when the DOD redirected $5M of Army Research, Development, Test, and Evaluation funding for CDMRP to initiate the ALSRP as a broadly competed, peer-reviewed research program. The ALSRP was not funded in FY08, but in FY09, Congress specifically appropriated funding for the ALSRP and has continuously provided funding since then, with a total appropriation of more than $79M, including $10M in FY18. Through its award mechanisms and funding recommendations, the ALSRP supports innovative preclinical research to develop new treatments for ALS.

PROGRAM PORTFOLIO
The ALSRP has focused on awards that support preclinical development of therapeutics for ALS. 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 (IND). This includes studies on drug production, purity, stability, toxicology, pharmacokinetics, pharmacodynamics, and efficacy in cell and animal models.

"This is a particularly exciting time for drug discovery for ALS, with an increasing number of small and large biotech companies dedicating programs to the disease. Investment through the ALSRP is critical to provide the necessary support for academia and small biotech to drive their novel treatment approaches toward the clinic. In just a few years, with the support from this program, six very different treatment approaches progressed from early preclinical development into advanced development and/or clinical trials."

Lucie Bruijn
Programmatic Panel Member; Chief Scientist, ALS Association



FY07-FY17 ALSRP Portfolio Investment by SCS Code

MUSCLE-DERIVED GDNF: A GENE THERAPEUTIC APPROACH FOR PRESERVING MOTOR NEURON FUNCTION IN ALS

Clive Svendsen, PhD, Cedars-Sinai Board of Governors Regenerative Medicine Institute

The ALSRP supported Dr. Svendsen's research to investigate the therapeutic potential of glial cell line derived neurotrophic factor (GDNF) as a treatment for ALS. GDNF, a growth factor, promotes the survival of glial cells, which support motor neurons. While the original studies suggested delivering GDNF to the muscle, this route was shown not to be effective. Instead, targeting the brain gave better results in animal models. In ALS patients, glial cells in the brain become sick and die, causing the death of motor neurons and progressive paralysis. Under an ALSRP Therapeutic Development Award, Dr. Svendsen and his team used a combined approach of glial cells modified to release GDNF to treat ALS. Reprogrammed human neural progenitor cells, genetically modified to secrete GDNF, were subsequently transplanted into the brain cortices of animal models to monitor the effects on ALS development. ALS models with the transplanted cells were found to live 8% longer and were free of paralysis 10% longer than untreated animals. Motor neurons in the spine also survived longer in the experimental group. While these initial research results show promise, more preclinical studies are needed to determine which treatment levels may be adequate and safe. Concurrently, Dr. Svendsen and colleagues at Cedars-Sinai are conducting a clinical trial, funded by the California Institute for Regenerative Medicine, using an indirect approach with similarly reprogrammed GDNF-producing progenitor cells that are transplanted into the spinal cords of ALS patients. "This is a small safety trial to ensure the cells releasing GDNF do not have any negative effects on leg function," Svendsen said. "If safe, we plan a larger future trial to see if this therapy can improve strength in the treated leg." Protecting motor neurons and preserving their function could improve both the quality and length of life for patients diagnosed with ALS in the future.

A HIGH-THROUGHPUT PHENOTYPIC SCREEN FOR C9ORF72 ALS THERAPEUTICS USING PATIENT-SPECIFIC MOTOR NEURONS

Justin Ichida, PhD, University of Southern California

With support from an ALSRP FY14 Therapeutic Development Award (TDA) award, Dr. Ichida has developed a new way to study human ALS motor neurons. Specifically, he has developed a stem cell technology that successfully converts blood cells of C9ORF72 ALS patients into a cell culture model of C9ORF72 ALS motor neurons. Dr. Ichida has shown that these motor neurons from ALS patients die faster than normal motor neurons and that they recapitulate the "disease in a dish." Dr. Ichida is currently treating these motor neurons with 40,000 different compounds to see if there are any treatments that can increase ALS motor neuron survival. By the end of the study, Dr. Ichida hopes to have identified therapeutic leads to target the C9ORF72 mutation in ALS patients.

Research 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 Practice (GMP) methods

Research Mechanisms

Therapeutic Idea Award (TIA)

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

TDA

- 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.

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 lifetime transitions to independence and a better life for those with autism and their families.

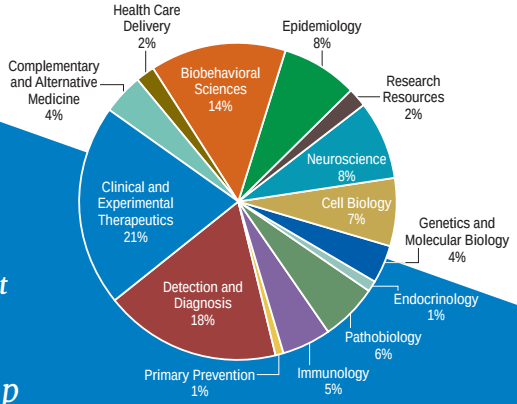
PROGRAM HISTORY

Since its inception in FY07, through FY18, appropriations totaling $81.9M 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.

"I was honored to represent the Ken Anderson Alliance on the FY17 ARP Peer Review Research Panel as an autistic adult consumer advocate. My experience with the ARP from the Department of Defense's Congressionally Directed Medical Research Programs has been tremendous. From the staff accommodations to the scientists' active engagement, it is clear that they want to understand the views of people with autism and what autistics hope to gain from research. This organization has impressed me and impressed upon me their commitment to including and advancing the conversations and cooperative endeavors between the scientists and the community their work is meant to serve."

Lori Hogenkamp

Ken Anderson Foundation, FY16 Consumer Reviewer



FY07–FY17 ARP Portfolio Investment by SCS Code


COGNITIVE ENHANCEMENT THERAPY: A PROMISING APPROACH FOR ADULTS WITH AUTISM SPECTRUM DISORDER

Nancy J. Minshew, MD and Shaun M. Eack, PhD, University of Pittsburgh

ASD-related neurocognitive impairments typically result in significant functional disability persisting throughout the lifetimes of those affected, impacting employability, relationship development, and diminishing overall quality of life. Drs. Nancy Minshew and Shaun Eack, with support from an FY10 ARP Clinical Trial Award, conducted the first randomized, controlled clinical trial evaluating the efficacy of Cognitive Enhancement Therapy (CET) on cognitive and behavioral deficits in verbal adults with ASD. CET was compared to Enriched Supportive Therapy (EST), an active comparison condition focused on psychoeducation and stress management, in 54 verbal adults with ASD. After 18 months of treatment, both therapies demonstrate gains, although CET produces more substantial improvements in social and non-social cognition, specifically attention and processing speed. Participants who received CET were more likely to be employed at the end of treatment compared to those who received EST. Approval from the Centers for Medicare and Medicaid Services to utilize CET as a standardized therapy for ASD requires confirmation of these results in a second, larger clinical trial funded by the National Institute of Mental Health, which is due for completion in 2020. Drs. Minshew and Eack are hopeful that there can be combined centers delivering CET and EST to facilitate the development and maintenance of the expertise and cross talk needed to address diagnostic difficulties and reduce social and cognitive impairments in adults with ASD through effective evidence-based treatments.


UNDERSTANDING THE CONSEQUENCES OF AGING IN AUTISM SPECTRUM DISORDER

Leslie C. Baxter, PhD, Barrow Neurological Institute, St. Joseph's Hospital and Medical Center, Phoenix, AZ and Christopher Smith, PhD, Southwest Autism Research & Resource Center, Phoenix, AZ

There is a pressing need to characterize the effects of brain aging in persons diagnosed with ASD to determine optimal treatment and care as these individuals are now reaching old age. With support from an FY14 ARP Idea Development Award (IDA), Drs. Leslie Baxter and Christopher Smith sought to understand the cognitive, behavioral, and neurological aspects of ASD in middle-aged men through neuropsychological tests to examine the differences between a group of high-functioning ASD men (aged 40-62 years) and a group of neurotypical (NT) men matched by age, IQ, and education. Results demonstrated that men in the ASD group made more errors than the men in the NT group during the performance of executive function-related tasks. Functional magnetic resonance (MR) neuroimaging of task-related brain networks revealed that functional connectivity in the working memory network, in the default mode network, and in the salience network were equivalent between the ASD and NT groups. However, MR neuroimaging showed that the cortico-striatal-thalamic-cortical circuitry network, which is involved in regulating attention and activity, was engaged in the NT group, but only minimally engaged in the ASD group. A model of ASD in older persons predicts greater impairment in executive function and frontal lobe susceptibility to dysfunction. This understanding can aid in developing care and treatment for the aging population of persons with ASD.

SUCCESSFULLY TRANSITIONING TO ADULTHOOD

An FY17 Clinical Translational Research Award was recently awarded to Dr. Amie Duncan at Cincinnati Children's Hospital Medical Center. Dr. Duncan will conduct a clinical trial assessing the effects of Surviving and Thriving in the Real World, a group-based intervention for high functioning adolescents with ASD that targets the development of daily living skills (DLS) such as hygiene and self-care, laundry, cooking, grocery shopping, and money management. High-functioning adolescents with ASD have impaired DLS that affect their ability to successfully transition to adulthood in the areas of education, employment, and independent living. The project will also explore the effects of social communication skills, executive functioning abilities, and parenting factors on the ability to acquire DLS. This work provides the initial steps in the development of an evidence-based DLS intervention package for teaching high functioning adolescents with ASD age-appropriate DLS to improve current and future adult outcomes.

Bone Marrow Failure Research Program

VISION

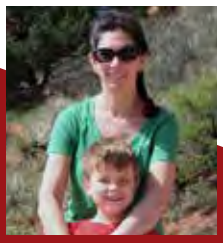
To understand and cure bone marrow failure diseases.

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.

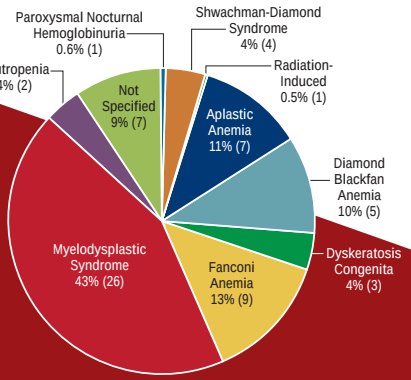
PROGRAM HISTORY

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 where somatic genetic mutations lead to a deficiency in hematopoiesis that presents itself in childhood or early adulthood. Acquired BMF includes a group of diseases that can occur following an environmental exposure such as ionizing radiation, chemical contamination, or the long-term effects of chemotherapeutics. Both types of BMF lead to life-long chronic illnesses with the potential to develop cancer. The Bone Marrow Failure Research Program (BMFRP) was initiated in FY08 to provide support for exceptional innovative research focused on BMF diseases. From FY08 through FY17, $32.55M has been appropriated by Congress to research the prevention, causes, and treatment of BMF diseases. The appropriation for FY18 for the BMFRP is $3M. Thus far, the BMFRP has invested in 65 awards, with the mission to support innovative research committed to advancing the understanding of inherited and acquired BMF diseases.

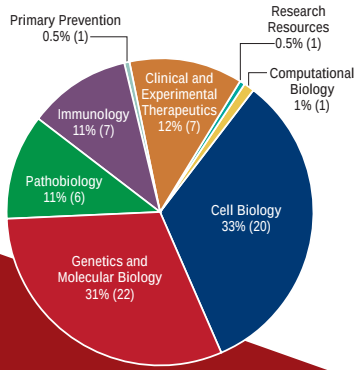


"I am honored to be a member of the BMFRP. The researchers and consumer reviewers who participate are profoundly dedicated to the research and to the patients. These are rare diseases, they suffer from a lack of pharmacological interest. That's what makes the BMFRP so important. It provides a consistent mechanism that BMF investigators can turn to for funding."

Deborah Cook
Programmatic Panel Member, FY14-FY18



FY08-FY17 BMFRP Disease Classification*



FY08-FY17 BMFRP Portfolio Investment by SCS Code*

**** Percentages of total spent, (number of awards).***

NOVEL THERAPEUTIC APPROACHES TARGETING MDSC IN MYELODYSPLASTIC SYNDROME

Sheng Wei, MD, Moffitt Cancer Center

Myeloid-derived suppressor cells (MDSCs) are immune regulator cells that originate in the bone marrow (BM). Aging-associated inflammation triggers MDSC expansion. These cells then induce cell death in BM stem cells, contributing to myelodysplastic syndromes (MDS) pathogenesis. Secreted inflammation-associated signaling molecules, such as S100A9, through interaction with the MDSC receptor CD33, have been identified as mediators of MDSC activation. Dr. Wei was awarded an FY14 BMFRP IDA to explore the possibility of targeting the S100A9-CD33 pathway to inactivate MDSCs. To accomplish this, an antibody of CD33, BI 836858, was used to block CD33 signaling. MDS BM primary specimens were treated with BI 836858, resulting in a significant reduction in the MDSC population and MDSC disease-promoting properties. BI 836858 treatment also demonstrated the potential to restore the hematopoietic capability of MDS BM-derived stem cells ex vivo. These results demonstrate the potential for targeting MDSCs to improve hematopoiesis in MDS patients. Currently, a Phase I clinical trial for BI 836858 treatment in MDS is ongoing.

A NOVEL THERAPY FOR TARGETING ACQUIRED BONE MARROW FAILURE DISEASES

Omar Abdel-Wahab, MD, Memorial Sloan Kettering Cancer Center;

Robert Bradley, PhD, Fred Hutchinson Cancer Research Center

Many patients with MDS progress to a rapidly growing cancer called acute myeloid leukemia (AML). Treatment options are often limited due to patient age and poor health. With support from the BMFRP through a FY15 IDA, Drs. Bradley and Abdel-Wahab sought to develop therapeutic approaches to target the spliceosomal mutant MDS. They focused on the most commonly mutated spliceosomal gene in MDS, Srsf2. They hypothesized that treatment of MDS spliceosomal gene mutant cells with a spliceosome inhibitor drug, E7107, may cause an overwhelming amount of splicing dysregulation, rendering them defective. Results demonstrate that the combination of Srsf2 mutation and E7107 treatment had larger implications on splicing in the mutant cells – implications that resulted in their cell death and decreased leukemic burden in Srsf2-mutant patient leukemia models. Excitingly, these results have contributed to a Phase I clinical trial (NCT02841540). The use of a splicing inhibitor such as E7107 could provide alternative, less invasive, and less intensive treatment of malignancies with splicing mutations.

UNDERSTANDING THE IMMUNE-MEDIATED T CELL RESPONSE IN APLASTIC ANEMIA

Yi Zhang, MD, PhD, Temple University of the Commonwealth System

Aplastic anemia (AA) is caused by the destruction of BM stem cells by immune-responsive T cells. BM transplantation has significantly improved the survival of AA patients. However, graft-versus-host disease (GVHD), a condition that occurs when the donor cells attack the patient's healthy tissues, poses a major barrier to transplantation success. Dr. Zhang obtained funding though a BMFRP FY10 New Investigator Award and FY15 IDA to elucidate the immune-mediated T cell response contributing to AA and GVHD. Dr. Zhang identified critical roles for histone modifier proteins in T cell pathways. Conditional loss of the histone methyltransferase, Ezh2, in donor T cells inhibited GVHD in a mouse model after BM transplantation. Most recently, Dr. Zhang has discovered a novel and clinically relevant pharmacological approach to target Ezh2 for preventing and treating GVHD. Currently, the regulation pathway initiated by the histone demethylase, Jmjd3, is being investigated for its role in controlling T cell immune responses. These results suggest multiple histone modifying proteins that could present therapeutic strategies for controlling the inflammatory T cells that contribute to AA and GVHD.

Breast Cancer Research Program

VISION
A world without breast cancer.

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

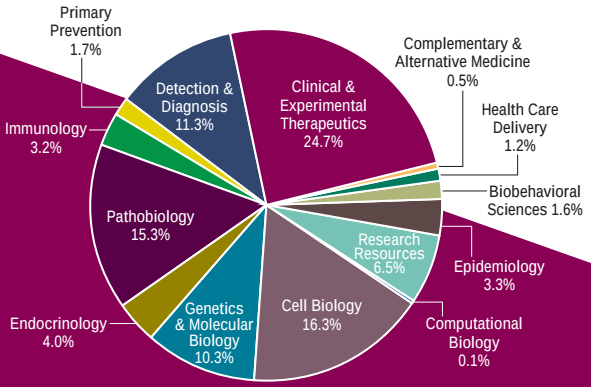
PROGRAM HISTORY
The Breast Cancer Research Program (BCRP) plays a leading role in the fight against breast cancer. The BCRP was established in 1993 as a result of the passionate efforts of breast cancer advocates. Their continued efforts, in concert with the program's successes, have resulted in more than $3.4B in congressional appropriations through FY18.

OVERARCHING CHALLENGES
Despite the significant progress that has been made in the breast cancer field since 1993, 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. To meet this urgent need, the FY18 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

"The DOD BCRP is a unique entity. It encourages researchers to dream big and think "outside of the box" to find ways to reduce death from breast cancer."

Michelle Esser
Consumer Reviewer



FY92-FY17 BCRP Portfolio Investment by SCS Code

NEW CLINICAL TRIALS IN 2018


TARGETING FATTY ACID SYNTHASE (FASN)

Ruth Lupu, PhD, and Tufia Haddad, MD, Mayo Clinic

FASN is an enzyme that is overexpressed in 30% of human epidermal growth factor receptor 2 (HER2)+ breast cancers. A novel, first-in-class FASN inhibitor, TVB-2640, was recently tested in a Phase I clinical trial (NCT02223247) and shown to have a favorable safety profile. The BCRP is now supporting a Phase II clinical trial (NCT03179904), of TVB-2640 in HER2+ metastatic breast cancer patients to determine whether FASN inhibition can restore tumor sensitivity to trastuzumab and paclitaxel, as well as to examine whether FASN expression in tumor specimens and serum could serve as a biomarker for prognosis and drug-resistance.

RESTORING THE ANTI-HER2 CD4 T-HELPER CELL (TH1) IMMUNE RESPONSE

Brian Czerniecki, MD, H. Lee Moffitt Cancer Center & Research Institute

HER2+ breast cancer patients that do not obtain a pathological complete response (pCR) after neoadjuvant therapy have been shown to lack a Th1 immune response against HER2+ tumor cells, which correlates with an increased risk of recurrence. The BCRP is supporting two clinical trials that aim to restore the anti-HER2 Th1 immune response to ultimately improve pCR and prevent disease recurrence. The first, a Phase II trial (NCT03384914), will determine whether a dendritic cell (DC1) vaccine or a DNA vaccine (WOKVAC) can prevent recurrence when given after neoadjuvant therapy in HER2+ patients with residual disease. The second, a Phase I trial (NCT03387553), will determine whether neoadjuvant DC1 vaccine in combination with chemotherapy can improve pCR.

BREAKTHROUGHS IN UNDERSTANDING THE MECHANISMS OF METASTASIS

TARGETING JAGGED1 TO TREAT BONE METASTASES

Yibin Kang, PhD, Princeton University

Jagged1 has been shown to promote tumor cell metastasis to the bone. The BCRP supported work demonstrating that treatment with cisplatin or paclitaxel could increase osteoblast expression of Jagged1, an observation that was also seen in patient samples post-chemotherapy. In bone metastatic mouse and cell models, Jagged1-expressing osteoblasts directly interacted with tumor cells and promoted tumor cell chemoresistance, which could be reversed using a novel Jagged1 blocking antibody 15D11. Administering 15D11 in combination with paclitaxel or cisplatin resulted in significant reduction in bone metastases and tumor cell colonization to the bone. Results from this study support further clinical development of 15D11 as an anti-metastatic agent.

Zheng H, Bae Y, Kasimir-Bauer S, et al. 2017. Therapeutic antibody targeting tumor- and osteoblastic niche-derived jagged1 sensitized bone metastasis to chemotherapy. *Cancer Cell* 32(6): 731-747.


MACROPHAGE ROLE IN EARLY BREAST CANCER DISSEMINATION AND METASTASIS

Nina Linde, PhD, and Julio Aguirre-Ghiso, PhD, Icahn School of Medicine at Mount Sinai

Macrophages have been shown to be recruited to breast cancer tumors, where they induce an EMT and motility in tumor cells. The BCRP supported work showing that macrophages recruited to the luminal epithelial layer of early breast lesions promoted loss of E-Cadherin in tumor cells, resulting in dissemination through the formation of tumor microenvironments of metastasis (TMEM). When macrophages were depleted in early lesions, E-Cadherin was found to be restored, and the number of TMEM and lung metastases were reduced. This work provides groundbreaking mechanistic insight into how cancer cells disseminate early and lead to metastases years after initial treatment of the primary tumor.

Linde N, Casanova-Acebes M, Soledad Sosa M, et al. 2018. Macrophages orchestrate breast cancer early dissemination and metastasis. *Nature Communications* 9(1):1-14.

Breast Cancer Research Semipostal Program

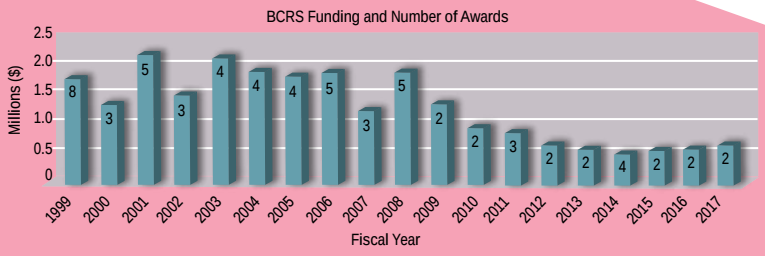
PROGRAM HISTORY

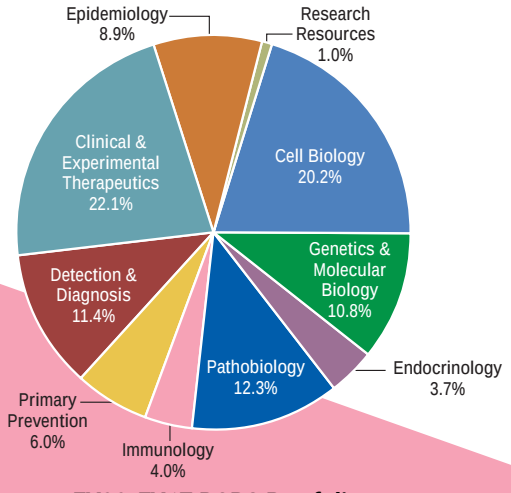
As a result of the efforts of breast cancer advocates, the Stamp Out Breast Cancer Act (Public Law 105-41) led to the US Postal Service's issuance of a new first-class stamp, the Breast Cancer Research Semipostal (BCRS) in 1998. It was the first semipostal in US history. Net revenues from sales of the 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 FY17 has been used to fully or partially fund 65 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 FY17)	$25,303,582.70
Research	$24,067,225.25
Management Costs	$1,236,357.45





FY99-FY17 BCRS Portfolio Investment by SCS Code

RESEARCH HIGHLIGHT

BREAST CANCER INTERRUPTS INTERFERON REGULATOR FACTOR 8 (IRF8)-DEPENDENT DENDRITIC CELL (DC) DEVELOPMENT IN ORDER TO EVADE THE IMMUNE SYSTEM

David DeNardo, PhD, Washington University

Tumors employ multiple mechanisms in order to evade the immune system or render immunotherapies ineffective. In a recent *Nature Communications* publication, Dr. DeNardo used breast cancer mouse models to show that conventional dendritic cells (cDCs; specifically cDC1) were downregulated in the bone marrow and blood serum. Importantly, these findings were also observed in breast cancer patients diagnosed with clinical stage II/III breast cancer. In addition, granulocyte-colony stimulating factor (GCSF) was found to be elevated in tumor tissue from mouse breast cancer models as well as breast cancer patients. In breast cancer mouse models, tumor-derived GCSF inhibited expression of IRF8, a transcription factor required for cDC1 differentiation, in pre-cDC progenitor cells located in the bone marrow. Furthermore, treating tumor-bearing mice with GCSF-neutralizing antibodies in combination with FMS-like tyrosine kinase 3 ligand (Flt3L) immunotherapy restored pre-cDC and cDC1 levels, as well as increased the number of tumor-specific cytotoxic T cells within the tumors. Results from this study suggest that pre-cDC and cDC1 levels in the blood and bone marrow could serve as prognostic and treatment response biomarkers for those diagnosed with breast cancer. Moreover, this study suggests that inhibition of GCSF may be necessary to effectively employ immunotherapy.

Meyer MA., Baer JM., Knolhoff BL., et al. 2018. Breast and pancreatic cancer interrupt IRF8-depndent dendritic cell development to overcome immune surveillance. *Nature Communications* 9:1250.

INNOVATIVE PROJECTS IN BREAST CANCER PREVENTION

RISK-ON-A-CHIP (ROC) FOR TAILORED PRIMARY PREVENTION OF BREAST CANCERS

Sophie Lelièvre, PhD, Purdue University

High mammographic density (i.e., dense breast tissue) and oxidative stress (OS) are considered risk factors for the development of breast cancer. With an FY16 Breakthrough Award Funding Level 1, Dr. Lelièvre and her collaborator, Dr. Ziaie, are developing a ROC assay that integrates engineering with state-of-the-art 3D cell culture, mimicking breast ducts and surrounding stroma. The ROC will be used to decipher how OS and breast density interact to lead to cancer onset. In the future, the team hopes that the ROC can be tailored to different risk(s) of interest and personalized to an individual, so that their cancer risk can be assessed and potential prophylactic approaches can be identified.

INHIBITION OF MICROBIAL B-GLUCURONIDASE (BGUS) AS A STRATEGY TOWARD PREVENTING BREAST CANCER

Sridhar Mani, PhD, Albert Einstein College of Medicine

It is well established that, in post-menopausal women, increased exposure to bioactive estrogen increases a woman's risk for developing breast cancer. Microbial BGUS has been shown to increase total bioactive estrogen in the body via enzymatically reactivating intestinal estrogen, allowing its resorption into circulation. Moreover, intestinal microbial BGUS levels have been shown to be higher in individuals who consume a high fat diet. With an FY16 Breakthrough Award Funding Level 1, Dr. Mani aims to test whether a specific microbial BGUS inhibitor, Inh9, could prevent reactivation and resorption of bioactive estrogen in the intestines, allowing its excretion and thus ultimately preventing breast cancer initiation and progression. If successful, this study will support the concept of inhibiting microbial BGUS as a breast cancer prevention strategy in high-risk women through either the use of selective microbial BGUS inhibitors or diet modulation.

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.

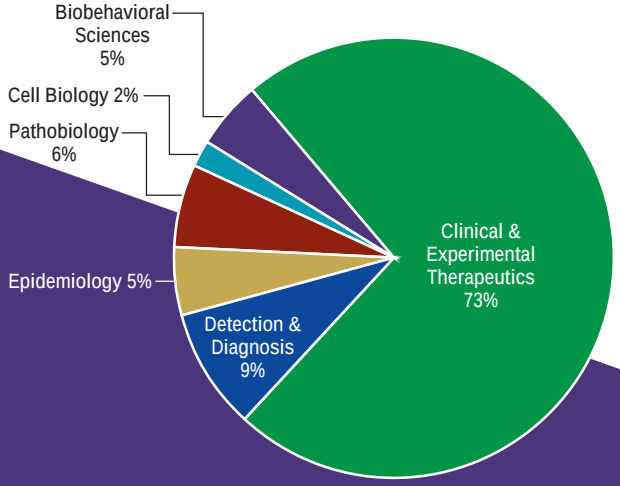
PROGRAM HISTORY

Duchenne affects approximately 1 out of every 5,000 male infants and about 20,000 new cases a year. This form of muscular dystrophy results from mutations in the dystrophin gene that leads to an absence of dystrophin in muscle cells, allowing these cells to be easily damaged. Duchenne mostly affects boys and reaches across all races and cultures. Duchenne is a severe, progressive disease that causes muscles to become weaker over time. Initially Duchenne presents between ages 2 to 6 with loss of ambulation by age 12. Loss of upper arm use quickly follows in the teenage years, and muscle weaknesses progress to heart and respiratory failure, eventually leading to death before or during an individual's 30s. Improvements in care for Duchenne over the last 10+ years have resulted in delayed progression of the disease.

The Duchenne Muscular Dystrophy Research Program (DMDRP) was established in FY11, the result of passionate and tireless advocacy efforts. The initial Congressional appropriation was $4M, and since that time, $26.4M has been appropriated to the program, including $3.2M in FY18. Currently, no treatment can stop or reverse the progression of Duchenne; however, during the past several years, research has identified many new potential therapeutic targets and significantly expanded the number of potential therapeutics in the pipeline for Duchenne. In order to assist in the development of treatments for Duchenne, the DMDRP has focused on accelerating promising therapeutic ideas into clinical applications and supporting the training of new physician researchers to facilitate their pursuit of careers in Duchenne research.

"We began our journey searching for information, seeking other families battling this disease, and traveling anywhere to receive the best care. As we learned more about Duchenne and as Duchenne began to take apparent effect on Wil's abilities, we began to focus on learning how to "live" with Duchenne and how to not let Duchenne define us.... I am grateful for the nomination by members of my extended [Duchenne] family as a Consumer Reviewer for the CDMRP. This role allowed me to represent the Duchenne community and truly advocate for all individuals living with Duchenne. My participation with the CDMRP strengthened my sense of hope. I truly believe that together, we will CureDuchenne!"

Tiffany Cook, **DMDRP Consumer Peer Reviewer**



FY11-FY17 DMDRP Portfolio Investment by SCS Code

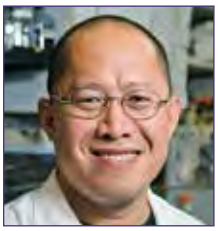
Duchenne muscular dystrophy (DMD) is a genetic disease caused by mutations in the dystrophin gene. The well-defined genetic cause of DMD makes it an excellent candidate for gene therapy approaches for treatment. Currently there are many gene therapies under development for DMD, such as delivering mini- or micro-gene dystrophin by viral vectors, genome editing, and oligonucleotide-mediated exon skipping. There are challenges to all of these gene therapy approaches and each has its own unique positive and negative attributes, thus all approaches require further research and optimization. Below are examples of two projects supported by the DMDRP investigating different gene therapy approaches.

MULTIPLEX CRISPR/CAS9-BASED GENOME ENGINEERING FOR THE GENETIC CORRECTION OF DUCHENNE MUSCULAR DYSTROPHY

Charles A. Gersbach, PhD, Duke University

Dr. Gersbach, with support from a Therapeutic Idea Award, explored developing methods to restore dystrophin expression via targeted genome editing in vivo using various DMD mouse models. The gene-editing technology CRISPR/Cas9 is an appealing alternative to gene replacement approaches for the correction of genetic diseases by representing a potential cure without the need for permanent integration of or repeated exposure to foreign biological material. In initial studies, adeno-associated virus (AAV) was used to deliver the CRISPR/Cas9 system to the mdx mouse model of DMD to remove the mutated exon 23 from the dystrophin gene. The deletion of exon 23 resulted in partial recovery of functional dystrophin protein in skeletal and cardiac muscle, improvement in muscle biochemistry, and significant enhancement of muscle force.

Next Dr. Gersbach explored translating CRISPR/Cas9 mediated genome editing methods to the human dystrophin gene; however, due to significant sequence diversity between the human and mouse DMD genes testing using current DMD mouse models was not possible, so Dr. Gersbach's team created a humanized diseased mouse model of DMD by deleting exon 52 from the human DMD gene in the previously characterized hDMD/mdx mouse. This hDMDΔ52/mdx mouse model lacked dystrophin protein expression and displayed a dystrophic phenotype. Using the hDMDΔ52/mdx mouse model a CRISPR/Cas9 mediated genome editing strategy that excised human dystrophin exon 51 in order to restore the reading frame was tested, and it restored expression of a functional, truncated dystrophin protein in both skeletal and cardiac muscle. This work advances the field of gene editing for neuromuscular disease and demonstrates a path for preclinical development of gene editing therapeutics for DMD in small animal models.



AAV VECTORS, A STEP TOWARD DUCHENNE MUSCULAR DYSTROPHY CLINICAL TRIALS

Dongsheng Duan, PhD, University of Missouri

Dr. Dongsheng Duan, with support from an Investigator-Initiated Research Award (IIRA), sought to engineer an AAV micro-dystrophin vector and then test the vector for body-wide gene therapy in a large mammal model of DMD. DMD is the most common lethal muscle disease, affecting 250,000 to 300,000 boys and young men worldwide. The muscle disease is due to the loss of an essential muscle protein called dystrophin. The AAV used in the study is a protein shell derived from a harmless virus called adeno-associated virus. A therapeutic gene can be encapsulated in this protein shell to become a gene therapy vector. Initial experiments confirmed that an AAV vector can lead to body wide gene transfer in a dystrophic canine model. Next, Dr. Duan injected his optimized AAV micro-dystrophin vector into young adult affected animals through the vein. Dr. Duan found that the optimized vector did not cause harm to dystrophic animals. Four months after a single-dose treatment, Dr. Duan found micro-dystrophin in every muscle in treated animals. When examined under a microscope, AAV micro-dystrophin treated muscle showed a much healthier look than untreated muscle. Dr. Duan has continued this promising work to determine how long therapeutic benefits can be maintained, and preliminary evidence from a partially DMDRP funded study suggests that a single-dose treatment with the optimized AAV micro-dystrophin vector does result in therapeutic benefits for at least 2 years without adverse reactions. Dr. Duan's efforts has provided the foundation for a collaboration with Solid Bioscience to initiate a clinical trial studying AAV micro-dystrophin gene transfer in adolescents and children with DMD (NCT03368742).

Epilepsy Research Program

VISION

The ERP envisions a time when the causative links between TBI and epilepsy are understood and PTE is both preventable and treatable.

MISSION

The ERP's mission is to advance research to understand the mechanisms underlying the genesis and progression of PTE, especially in Service members and Veterans.

PROGRAM HISTORY

The DOD Epilepsy Research Program (ERP) was established in FY15 to develop an understanding of the magnitude of PTE within the military and to expand research into the basic mechanisms by which TBI produces PTE. Epilepsy is the fourth most common neurological disorder[1] and can be found in the active duty military population.[2] Mild, moderate, and severe TBI are all linked to epilepsy,[3] but the nature of the connection remains vastly unexplored. Mechanisms and markers of pathology and population-based research are needed in order to understand the connection between TBI and epilepsy. These gaps are reflected in the FY18 ERP's focus areas, which change as the direction of the ERP evolves, and are summarized below.

Epidemiology: Epidemiological characterization of PTE following TBI, which may include studies of risk factors, differentiation of PTE and psychogenic non-epileptic seizures (PNES), and outcomes/morbidity.

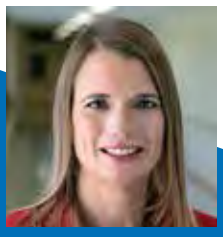
Markers and Mechanisms: Identifying markers or mechanisms that address PTE in terms of early detection, diagnosis, prognosis, morbidity, comorbidity, mortality, and risk stratification.

Longitudinal Studies: Studies of the natural evolution of PTE, which may include seizure frequency and severity, comorbidities, latency between injury and PTE, mortality, treatment, and the quality of life of individuals with PTE.

[1] Hirtz D, Thurman DJ, Gwinn-Hardy K, et al. 2007. "How common are the "common" neurological disorders?" *Neurology*. 68(5):326–337.

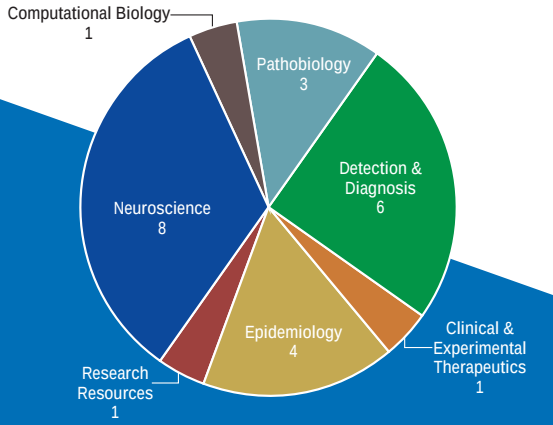
[2] Armed Forces Health Surveillance Branch. 2013. "Epilepsy in Active Component Service Members, 1998–2012." *Medical Surveillance Monthly Report*. 20(5):19–22.

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



"We are working to foster interdisciplinary investigation of the relationship between traumatic brain injury and the development of epilepsy, with particular interest in longitudinal epidemiological research. The panel's work will have a direct impact on Service men and women returning from the Persian Gulf Wars and Afghanistan as well as civilians who have sustained traumatic brain injury. The CDMRP has taken on this newly funded program with dedication and energy, and I am delighted to imagine the progress forward in the understanding of post-traumatic epilepsy."

Karen Parko
ERP Programmatic Panel Chair



FY15–FY17 ERP Portfolio Investment by SCS Code

ERP RESEARCH INVESTMENT

Between FY15 and FY17, the ERP has received $22.5M to fund research in PTE. The funding has resulted in 24 awards. Across the portfolio, ERP-funded research is examining (1) new and innovative animal models for evaluating the connection between TBI and PTE, (2) the differences between PTE and PNES, and (3) connectomics approaches to look at functional brain changes associated with PTE subsequent to TBI. This is in addition to epidemiological studies of Service members and several studies of PNES. Research into PNES is necessary in order to characterize the similarities and differences between PNES and PTE. This will provide a better understanding of both. For FY18, the ERP continues to fund needed and innovative research. This is the first year that the ERP will emphasize the need for longitudinal, population-based research studies. These studies may help the ERP understand how issues such as comorbidities and treatment figure into patient care and quality of life.

ERP PARTNERSHIPS

Research initiatives that will have an impact on populations affected by PTE require strong research funding partners. In 2015, the DOD provided funding to CURE to examine PTE. Research funded by CURE is often multidisciplinary by nature, and the CURE DOD PTE initiative allows grantees to regularly learn from each other. The DOD also closely partners with the National Institute of Neurological Disorders and Stroke, which has a significant grant portfolio on PTE, through a number of workshops and other meetings regarding PTE. These partnerships are key, as they allow public and private entities to use their differing scientific models to accelerate PTE research.

THE EPIDEMIOLOGY OF EPILEPSY AND TRAUMATIC BRAIN INJURY: SEVERITY, MECHANISM, AND OUTCOMES

Mary Jo Pugh, PhD, RN, South Texas Veterans Health Care System

While the link between severe TBI and epilepsy is well known, the long-term consequences of mTBI, the most common brain injury among post-9/11 Veterans, remain unclear with regard to PTE. To address this, Dr. Mary Jo Pugh was awarded an FY15 ERP IDA to examine the association between TBI and PTE in Veterans who were deployed in post-9/11 conflicts. By comparing the medical records of post-9/11 Veterans, Dr. Pugh and her team found that Veterans with mTBI were twice as likely to have epilepsy as Veterans without TBI. In addition, Dr. Pugh's group is conducting a national survey to examine the unique effects of mTBI and epilepsy on the social, emotional, and physical functioning of our Veterans. Dr. Pugh and her team will also collect advanced clinical, cognitive, and neuroimaging data from a subset of participants. Importantly, this study seeks to identify populations at highest risk for developing PTE after mTBI, which may lead to earlier identification and treatment. Additional outcomes may include identifying individuals who may benefit from non-pharmacological therapy, such as cognitive or lifestyle interventions. These types of interventions may benefit patients with PTE by improving their ability to manage their epilepsy, leading to better health outcomes for both patients and their families.

NEUROIMAGING BIOMARKER FOR SEIZURES

William Curt LaFrance, MD, MPH, Ocean State Research Institute

Soldiers are exposed to a number of physical and psychological stressors in combat that can have long-term consequences. TBI, commonly seen in Veterans, can lead to PTE, where patients suffer from epileptic seizures that are the result of aberrant neuronal activity. In addition, Veterans may suffer from seizures that are non-epileptic (PNES), which lack epileptiform activity on an electroencephalogram, but are otherwise comparable to epileptic seizures. PNES is thought to be the result of traumatic experiences, such as those seen in combat. With the help of an FY16 ERP IDA, Drs. LaFrance and Jerzy Szaflarski, and their colleagues are investigating the neural circuitry of PTE and PNES through a longitudinal neuroimaging study of Veterans. Specifically, Dr. LaFrance's team will perform MRI before and after patients receive cognitive and behavioral therapy for seizures, which in preliminary studies reduced seizure burden in patients with PNES. In addition, these findings will be compared to patients who have received a TBI, but have not had PTE or PNES. Dr. LaFrance and his team are working to find neural signatures that differentiate PNES from PTE and TBI in Veterans with the hope that these discoveries may lead to better treatments for both PNES and PTE.

Gulf War Illness Research Program

VISION

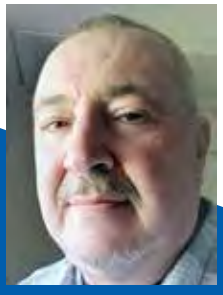
Improved health and lives of Veterans who have Gulf War Illness.

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.

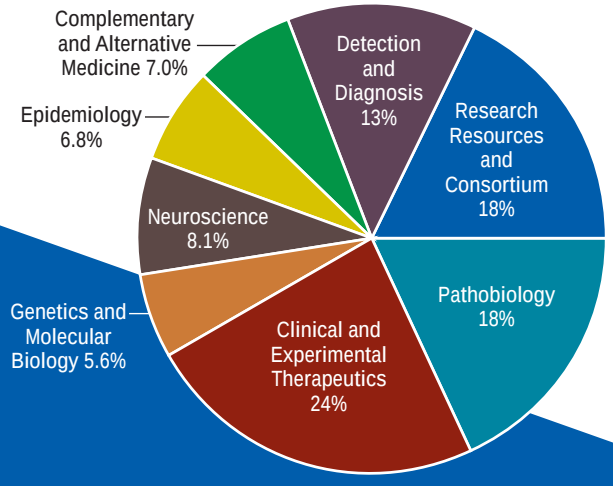
PROGRAM HISTORY

GWIRP was established in 2006 and renewed by Congress in 2008. Prior DOD-funded research into GWI was managed by the USAMRMC MOMRP or intermittently through CDMRP. Since FY06, GWIRP has received a total of $170M in Congressional appropriations, including $21M in FY18. 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. GWIRP funded two research consortia in FY12 primarily focused on mechanistic and translational research. In FY17, GWIRP funded two new major multi-institutional consortia that will design, develop, and execute collaborative Phase I and II clinical trials of promising therapeutic agents and develop a GWI biorepository focused on the collection, processing, annotation, storage, and distribution of clinical specimens and research data.



"I've been a consumer reviewer for five years. In that time, as technology has advanced exponentially, I've seen CDMRP-funded studies produce some very pertinent results. Each year I see new proposals build upon the results of the previous studies as researchers work to help our Veterans. Consumer reviewers bring the Veterans voice to the table and help focus the science on real human impact. Our opinions carry the same weight as the rest of the panel, allowing us to measure the impact in real life. This is a key part in why CDMRP is so important to our Veterans."

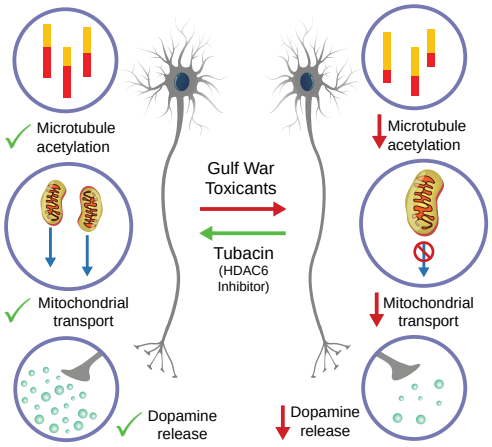
Peter Greene
Consumer Peer Reviewer



FY06–FY17 GWIRP Portfolio Investment by SCS Code

MICROTUBULE ABNORMALITIES UNDERLYING GULF WAR ILLNESS IN NEURONS FROM HUMAN-INDUCED PLURIPOTENT CELLS

Peter Baas, PhD, Drexel University



GWI is a chronic multisymptom illness that affects around one-fourth of Gulf War Veterans. Many of these Veterans are believed to have been exposed to organophosphate nerve agents, which can cause a wide range of neurological disorders and other ailments. Microtubule abnormalities are commonly present in Veterans suffering from GWI, making microtubule-based therapies a viable option for treatment. Development of effective treatments depends on animal models that neither share a similar genetic background nor consider epigenetic factors relevant to human disease. With support from a FY14 New Investigator Award, Dr. Baas sought to develop and establish a repository of self-renewing human-induced pluripotent stem cells (hiPSC) from blood samples of Veterans who suffer from GWI. The repository will serve as a cell bank to test possible therapies and develop microtubule-based approaches to correct the cellular defects present in GWI. In a recent paper published in *Traffic*, Dr. Baas showed that tubacin, a drug that inhibits a tubulin deacetylating enzyme (HDAC6), is able to correct some of the cellular abnormalities present in GWI. Based on this work, Dr. Baas suggested that HDAC6 may be a novel therapeutic target for Gulf War Veterans and he has been awarded a follow-up grant to continue his work by investigating the therapeutic potential of HDAC6 inhibitors on GWI.

A PROSPECTIVE OPEN-LABEL CLINICAL TRIAL OF METHYLPHENIDATE PLUS A GWI-SPECIFIC NUTRIENT FORMULA IN PATIENTS WITH GULF WAR ILLNESS AND CONCENTRATION DISTURBANCES

Jon Kaiser, MD, K-PAX Pharmaceuticals, Inc.

Many Gulf War Veterans experienced prolonged exposure to toxins while serving. In some, this toxicant exposure may have triggered a secondary mitochondrial disease, which may underlie or exacerbate GWI. Notably, GWI patients and those with known mitochondrial disease have overlapping symptoms, such as fatigue and cognitive dysfunction. Dr. Jon Kaiser and Dr. Mark Holodniy, with the support of an FY13 GWIRP Innovative Treatment Award, tested a combination treatment that is designed to support the mitochondria of the nervous system in an open-label clinical trial in patients with GWI. The treatment, known as KPAX002, combines a low dosage of the central nervous system (CNS) stimulant methylphenidate and a micronutrient formula intended to support mitochondrial metabolism. The combination of these two components supports the recovery of dysfunctional mitochondria in the nervous system leading to an improvement in clinical symptoms. Dr. Kaiser's team found that, after 12 weeks of KPAX002 treatment, patients had a 25% decrease in overall GWI symptoms. Additional clinical assessments revealed specific improvements in cognitive symptoms, pain, and sleep. Further, Dr. Kaiser's group found reduced levels of a biomarker for oxidative stress, suggesting improved mitochondrial function. These results suggest that remediation of mitochondrial dysfunction, in combination with the gentle stimulation of nervous system function, can improve symptoms experienced by Veterans with GWI.

Hearing Restoration Research Program

VISION

Improve the operational performance, medical readiness, and quality of life of Service members and Veterans with auditory system injuries.

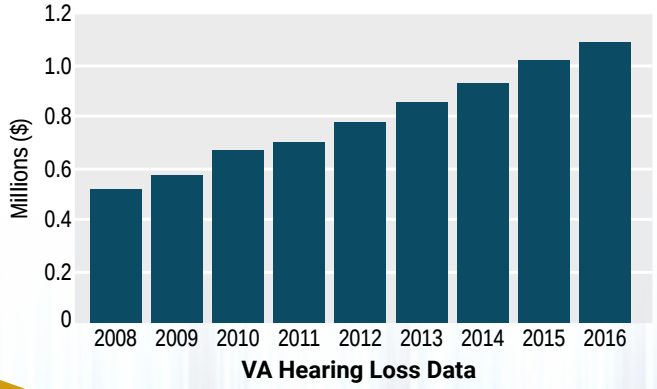
MISSION

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 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 Veterans Benefits Administration, VA 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.

HEARING LOSS PREVALENCE



VA Hearing Loss Data

Cumulative numbers of Veterans with disabilities due to Service-connected hearing loss. Based on data from the *Veterans Benefits Administration Annual Benefits Report Fiscal Year 2016.*

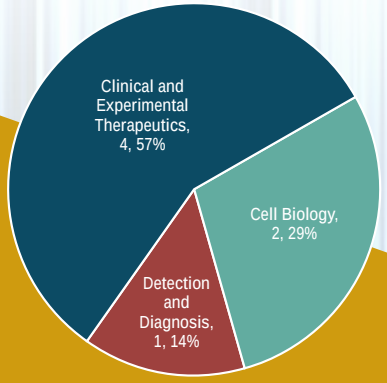
FY18 AWARD MECHANISMS

Translational Research Award (TRA)

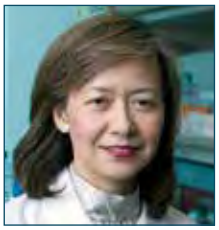
The FY18 HRRP TRA mechanism is intended to support translational research that will accelerate the movement of promising laboratory research relevant to hearing restoration into clinical applications.

Focused Applied Research Award (FARA)

The FY18 HRRP FARA mechanism is intended to support applied research that will advance the diagnosis and treatment of auditory dysfunction where hearing sensitivity may be within normal limits, but the individual's capacity to listen and understand speech is substantially impaired.



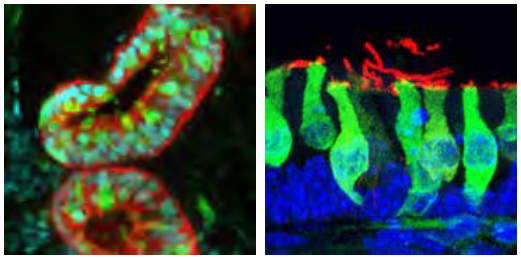
FY17 HRRP Portfolio Investment by SCS Code (Number of Awards and Percentage of Total Investment)



HUMAN INNER EAR ORGANOIDS AS AN IN VITRO MODEL FOR HEARING THERAPY DEVELOPMENT

Eri Hashino, PhD, Indiana University School of Medicine

The inner ear is one of only a few organs for which biopsy is not applicable, severely limiting the availability of human tissues for the testing of potential therapeutics. Dr. Hashino, a recipient of FY17 HRRP TRA, is leading the research effort to overcome this critical problem. Dr. Hashino's team has recently established a novel means to generate inner ear sensory epithelia from human pluripotent stem cells in 3D culture. These stem cell-derived tissues, designated as "human inner ear organoids," harbor a layer of tightly packed hair cells whose structural, biochemical, and functional properties are indistinguishable from native sensory hair cells in the human inner ear. With funding from the HRRP TRA, Dr. Hashino will develop the human inner ear organoids technology to the next level. Her team will establish and validate the organoids as a novel in vitro model to recapitulate human cochlear development and degeneration, elucidating the signals and genetic pathways underlying cochlear hair cell induction and differentiation. Additionally, the organoids will be used as a human in vitro model to test the ability of a small molecule inhibitor to promote hair cell differentiation and regeneration. If successful, the human inner ear organoids technology will offer unprecedented opportunities to discover therapeutic targets and test therapeutic agents to restore hearing.

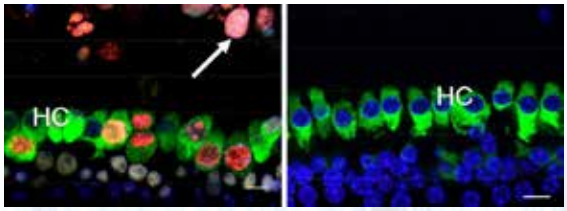


Left Panel: Human stem cell-derived inner ear organoids containing hair cells. EPCAM (Red), PCP4 (Green), SOX2 (Cyan); **Right Panel:** Stem-cell derived hair cells with stereocilia bundles. CALRETININ (Green), ESPIN (Red), DAPI (Blue)

HAIR CELL REGENERATION IN MATURE MAMMALIAN INNER EAR

Zheng-Yi Chen, PhD, Massachusetts Eye and Ear Infirmary

The mature mammalian inner ear is not responsive to regenerative signals that have proven successful in young inner ears that are still undergoing development. This suggests that most of the developmental pathways that render inner ear responsive to hair cell induction are no longer available in the mature inner ear. With support of a FY17 HRRP Translational Research Award, Dr. Chen aims to tackle this problem. Dr. Chen will utilize a strategy known as "reprogramming" to re-set the biological clock of mature inner ear and turn them into a stage reminiscent of young inner ear, so that the mature inner ear cells regain the capacity to respond to regenerative signals. Previous work by Dr. Chen's team indicate that it is feasible to reprogram adult cochlear cells, evidenced by cell cycle re-entry, activation of otic genes, and the ability for transdifferentiate supporting cells to hair cells. Capitalizing on this knowledge and on the team's expertise in adult whole cochlea explant culture, in vivo injection, and transgenic mouse models, Dr. Chen will test a strategy to reprogram mature and aged mammalian cochlea by the transient and reversible co-activation of two critical genes. The reprogrammed inner ear will be evaluated for hair cell regeneration and hearing recovery in response to hair cell induction signals in a mouse model of noise-induced hearing loss. The approach can also be applied to regenerate other inner ear cell types critical for hearing in adult cochlea. If successful, the study will provide significant conceptual and practical advance toward the goal of hearing restoration in human patients.



Left panel: After activation of MYC and Notch pathway, adult mouse cochlear hair cells (green - MYO7A) and supporting cells (grey - SOX2) were induced to proliferate (red - EdU labeling). A proliferating supporting cell is indicated by arrow. **Right panel:** In control adult mouse cochlea without MYC or Notch activation, no proliferation was induced. HC: hair cells. Scale bars: 10μm

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 JWMRP provides the DOD with a powerful tool for advancing previously funded Congressional Special Interest (CSI) 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 JPC/PAD 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, and FY18. Because the overall goal of the program is to deliver a product for the DOD, the ratio of funding over the past 4 years has intentionally reduced the percentage of funds directed toward early technology development and increased the proportion of funding for advanced technology development initiatives. A total of 28 projects were funded by JWMRP in FY12, 35 in FY13, 46 in FY14, 30 in FY15, 34 in FY16, and 26 projects in FY17. The graph on the next page depicts the program investments for FY17.

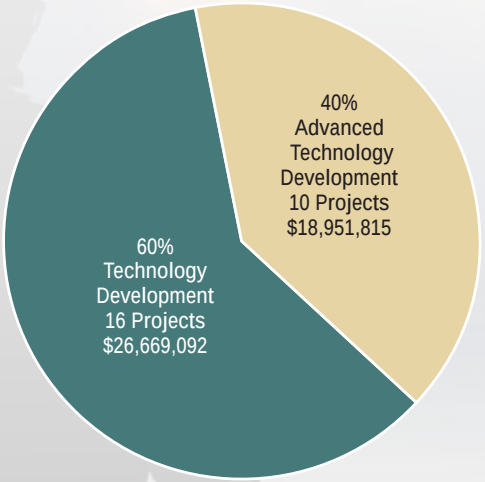
JWMRP is a dynamic program that facilitates the maturation of previous congressionally funded research efforts that demonstrate the potential to close identified military medical capability gaps. By focusing on both early and advanced technology development, JWMRP provides a pathway to transition products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

A Focused Effort on Improving Cognitive and Functional Deficits after TBI Using Virtual Technology
Ultra Wide-Band Wearable Ultrasound Probe for Battlefield Use
Phase II b Clinical Trial for a Norovirus Vaccine
Phase II Malaria Clinical Trial with the First Live Attenuated Vaccine Against Protozoal Disease in Humans
Development and Clinical Trial of a Food Supplement to Prevent Travelers' Diarrhea
Development of a Lyophilized Injectable for Point-of-Care Therapeutic for Post-Traumatic Osteoarthritis
Development of an Effective Exposure Psychotherapy Paradigm for the Treatment of Post-Traumatic Stress Disorder
Device Development of the Transportable Pathogen Reduction and Blood Safety System
Development of a Non-Electric, Disposable IV Infusion Pump
Pivotal Study on the Regulatory Approval Pathway for a Drug to Treat Acute Radiation Sickness
Accelerating the Development of the Opioid Sufentanil for Pain Treatment
Development of Electronic Capture and Seamless Communication of Point-of-Injury Information Using Ultra-Wide-Band Technology Integrated with Nett Warrior Platform
Development of Bioengineered Corneas for Transplantation
Light-Activated Sealing to Improve Outcomes Following Penetrating Bowel Trauma
Non-Invasive Intracranial Pressure Assessment Using a Compact Portable Monitor
Development of an Implantable Pudendal Nerve Stimulator to Restore Bladder Function in Humans After Spinal Cord Injury

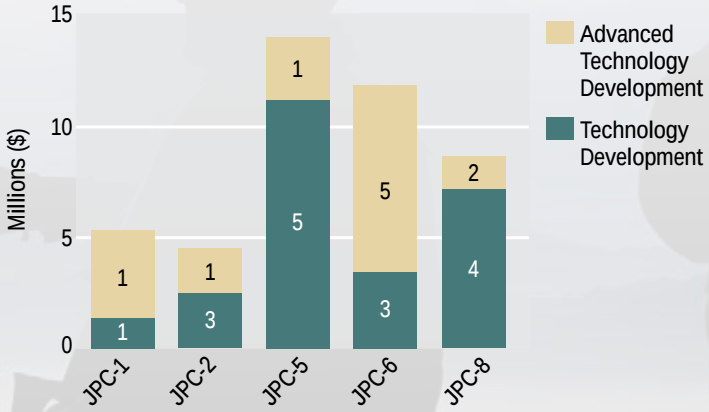
Prosthetic with Moisture Management Liner and Active Cooling System

Ultrawide-Band, Wearable Ultrasound Probe for Battlefield Use

Non-Invasive Intracranial Pressure Assessment



FY17 JWMRP Investment



FY17 JWMRP Final Funding Distribution (Number of Awards Granted Indicated in Each Bar Chart)

Kidney Cancer Research Program

VISION

To eliminate kidney cancer through collaboration and discovery.

MISSION

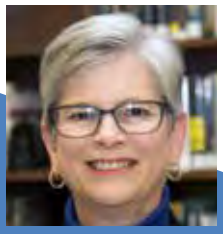
To promote rigorous, innovative, high impact research in kidney cancer for the benefit of Service members, Veterans, and the American public.

PROGRAM HISTORY

The US Congress in FY17 appropriated $10M for research into kidney cancer, thus establishing the KCRP. For FY18, the KCRP appropriation is $15M. The American Cancer Society estimates that, in 2018, approximately 63,340 new cases of kidney cancer will occur, and 14,970 people will die from some form of kidney cancer.[1] The 5-year survival rate of patients diagnosed with stage I kidney cancer is 92.6%, while for patients diagnosed at stage II, it is 68.7%.[3] KCRP focuses on research into the prevention, detection, and treatment, and patient quality of life.

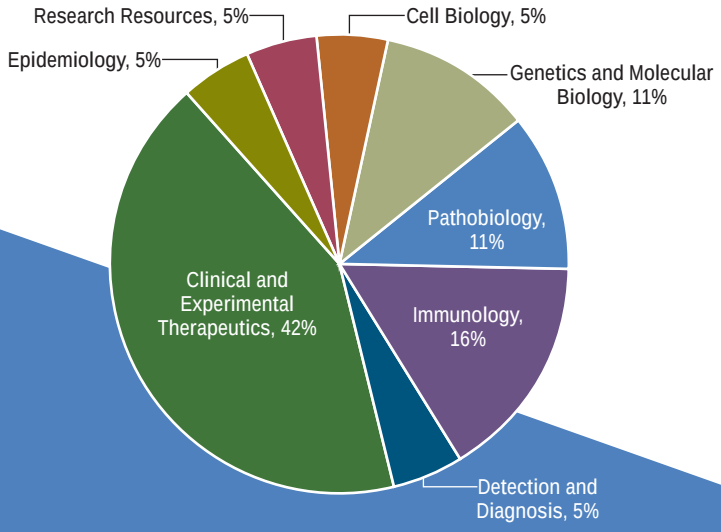
In the inaugural year, the KCRP offered funding opportunities through mechanisms focused on innovation (Concept and IDA) as well as mechanisms intended to expand clinical outcomes (Translational Research Partnership Award and the Consortium Development Award). Twenty outstanding applications will be funded to launch the kidney cancer research under CDMRP's tradition of excellence.

[1] https://www.cancer.org/cancer/kidney-cancer/about.html
[2] https://www.cancer.gov/types/kidney
[3] https://seer.cancer.gov/statfacts/html/kidrp.html



"It has been my experience that when patients and consumers as well as scientists, researchers, physicians, and clinicians are all around the table, understanding and respect is quickly achieved. A win-win for all involved."

Sarah Wise Miller
Kidney Cancer Association
FY17 KCRP Peer Review
Consumer Reviewer



FY17 KCRP Portfolio Investment by SCS Code

KIDNEY CANCER CLINICAL TRIALS CONSORTIUM

Eric Jonasch, MD, MD Anderson Cancer Center (Houston)

There has been a growing appreciation for the importance of personalized medicine in the treatment of cancer. However, the primary goal of many clinical trials sponsored by pharmaceutical companies is to obtain drug approval. Although these trials are important, they do not address the critical need for clinical trials that focus on developing the novel strategies, biomarkers, and treatment combinations necessary for a personalized therapeutic approach.

With the goal of establishing a multi-center consortium to address these needs in kidney cancer patients, Dr. Eric Jonasch was awarded the FY17 Consortium Development Award. Dr. Jonasch has assembled a team of kidney cancer clinicians to build a unique consortium: Dr. David McDermott at Beth Israel Deaconess Medical Center in Boston, Dr. Hans Hammers at University of Texas Southwestern Medical Center in Dallas, and Dr. Moshe Ornstein at The Cleveland Clinic Foundation in Cleveland. Historically, multi-center clinical trials were not feasible due to myriad bureaucratic and technical hurdles. This team will spend the next 2 years breaking down the traditional barriers to multi-site clinical trials. These efforts will include developing a protocol approval process that is harmonized across all consortium sites, putting into place agreements to facilitate contracting agreements, and developing data management and sample analysis infrastructure consortium-wide. At the conclusion of the Consortium Development Award, Dr. Jonasch and his team will be poised to start active recruitment for new kidney cancer clinical trials.

USING SINGLE CELL TRANSCRIPTOMICS TO UNDERSTAND TUMOR AND IMMUNE HETEROGENEITY

Michael Atkins, MD, Georgetown University and Catherine Wu, MD, Dana Farber Cancer Institute

Solid tumors, such as renal cell carcinoma, exist in a complex, heterogeneous environment that includes tumor cells, immune cells, the extracellular matrix, and other components. Until recently, the primary method of surveying tumor samples was to perform bulk analyses. This involves analyzing a small portion of a tumor as a homogenous sample without attempting to break it down into the individual components. However, all of these are distinct cellular populations that contribute uniquely to therapeutic response and the development of therapeutic resistance.

Dr. Michael Atkins of Georgetown University is a translational research leader in the field of kidney cancer. Dr. Catherine Wu is an expert in tumor heterogeneity and has significant experience in developing methods to study tumor heterogeneity at the single cell level. These two will team up for an FY17 Translational Research Partnership Award to study the role of tumor and immune heterogeneity in developing therapeutic resistance to the immunotherapeutic Nivolumab at the single cell level. Drs. Atkins and Wu believe that understanding the mechanisms of resistance will lead to the development of personalized treatment regimens that expand the potential of immunotherapy to more kidney cancer patients.

"When my husband lost his battle to kidney cancer at the age of 45, the landscape for research in kidney cancer looked bleak. There weren't many therapeutic options available, and kidney cancer just didn't seem to be a focus at many cancer centers. Today, I have a great sense of optimism for the future. Being part of the Kidney Cancer Research Program has fueled that hope. The KCRP brings doctors, researchers, and patients together to ... accelerate research for a cure. While it won't make a difference for my husband - it might make a difference for our daughters. They carry his genes."

Dena Battle
President, Kidney Cancer Research Alliance (KCCure)

Lung Cancer Research Program

VISION

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.

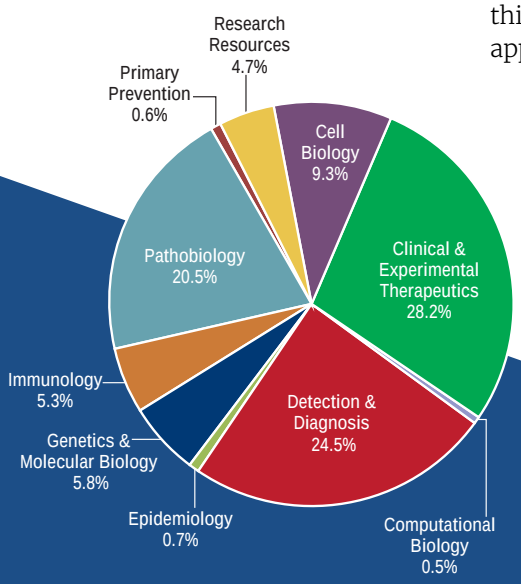
PROGRAM HISTORY

The DOD LCRP was established in FY09 with a congressional appropriation of $20M as a result of the passionate efforts of lung cancer advocates. Their continued efforts along with the LCRP's critical role in helping to accelerate high-impact research, encouraging innovation and stimulating creativity, bringing new investigators into the lung cancer field, and facilitating the creation of unique partnerships and resources have resulted in more than $127M in congressional appropriations through FY18.

AREAS OF EMPHASIS

The LCRP recognizes that there are a broad range of unanswered research questions potentially critical to advancing prevention, detection, treatments, and cures for lung cancer. In studying these critical unanswered research questions, it is clear that the LCRP plays a unique role in funding lung cancer research that will enable breakthroughs that will save lives and lead to the eradication of deaths and suffering from this disease. To address this urgent need, the FY18 LCRP requires all applicants to address at least one of the following areas of emphasis:

- Identify, develop, or optimize noninvasive or minimally invasive tools to improve the detection of the initial stages of lung cancer
- Identify, develop, and/or build upon already existing tools for screening or early detection of lung cancer
- Understand the molecular mechanisms of initiation and progression to clinically significant lung cancer
- Identify innovative strategies for prevention and treatment of lung cancer
- Understand predictive markers to identify responders and nonresponders
- 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



FY09-FY17 LCRP Portfolio Investment by SCS Code

ANTIDIABETIC DRUGS ARE A POTENTIAL SOLUTION TO SOME TREATMENT-RESISTANT TUMORS

Melin Khandekar, MD, PhD, Massachusetts General Hospital

One of the biggest challenges facing oncologists today is the development of treatment-resistant tumors. In many cases, a patient who starts off a treatment regimen with a positive response and tumor reduction experiences significant setbacks when the cancer develops resistance to the primary therapeutic. One approach to overcoming treatment resistance is to use a combination of therapies at the start of treatment to increase the sensitivity of the tumor to common therapeutics. This allows a chance for the original therapy to work before the tumor is able to adapt and develop resistance. Dr. Melin Khandekar, a LCRP researcher at Massachusetts General Hospital, is using this approach to improve tumor response to commonly used chemotherapies.

Previous work at Dr. Khandekar's institution revealed that tumor cells tend to overexpress the peroxisome proliferator activator receptor-γ (PPARγ), a receptor protein that plays a key role in metabolism and is a popular target for antidiabetic drugs. Because of this overexpression, tumor cells were sensitized to treatment by targeting PPARγ using thiazolidinedione (TZD) class drugs, a common antidiabetic. Unfortunately, TZDs have fallen out of use due to concerns about possible side effects. Through a Career Development Award from the LCRP, Dr. Khandekar's work is focusing on testing the effectiveness of TZD alternatives and confirming that targeting PPARγ with these new compounds sensitizes cancer cells to carboplatin chemotherapy.

In a paper recently published in the *Proceedings of the National Academy of Sciences*, Dr. Khandekar shares his most recent findings. He first confirmed that one contributor to chemotherapy/DNA damaging agent resistance is the phosphorylation of an amino acid on PPARγ. Upon exposure to carboplatin, cancer cells respond by phosphorylating a serine residue (S273) of PPARγ. This decreases the cells' accumulation of DNA damage when exposed to chemotherapy, preventing cell death. Dr. Khandekar and his team confirmed that blocking the phosphorylation of S273 restores the accumulation of DNA damage from the chemotherapeutic agent, leading to apoptotic cell death. He approached this in two ways. The first was to mutate the serine that was being phosphorylated to an alanine (S273A). This mutation retains the activity of PPARγ, but prevents phosphorylation. The second approach used novel noncanonical agonist ligands (NALs), TZD alternatives, to inhibit the phosphorylation. Both techniques successfully resensitized the cancer cells to cytotoxic agents that directly target DNA and cells responding well to the combination treatment demonstrated a specific gene signature that is predictive of chemotherapy response and patient outcome.

While a number of steps still need to be taken before these NALs are an option for patient treatment, this preclinical work shows significant promise. Because NALs are also appealing as potential antidiabetic drugs, they are more likely to be available to cancer patients sometime in the near future.

"Lung cancer claims more lives than any other cancer in the United States and affects military Veterans at higher rates than the general population. As chief of the Hematology/Oncology Service at Walter Reed National Military Medical Center, I have directed the care of lung cancer patients who have served in every major war since WWII. As a doctor deployed to OIF, I have shared the same exposures that lead our newest Veterans to fear for their future health. The work of the LCRP is essential for all those touched by this disease. The collaborative reviews by academic, federal government, military, and the VA experts ensure that funding is directed to the best science with highest potential impact. Only through such steadfast advancements in medical science will we be able to prevent future deaths and improve the lives of those living with lung cancer right now"

LTC David Van Echo
LCRP Programmatic Panel Chair

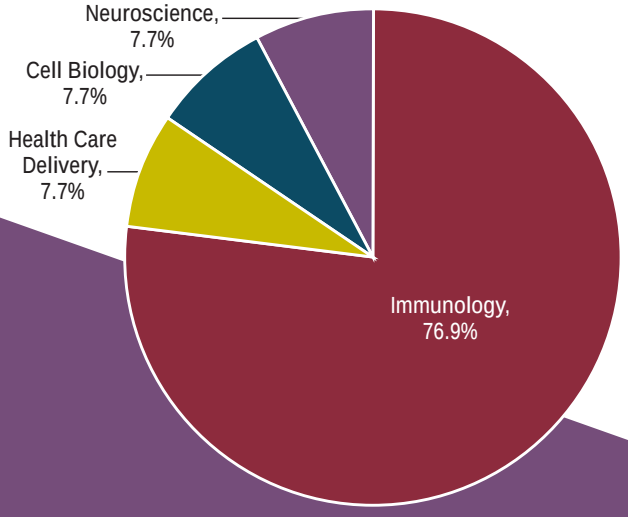
Lupus Research Program

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. Women are at a greater risk of developing lupus than men, and women of color are two to three times more likely to develop lupus than 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. 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 (PRMRP) from FY05–FY16. During this time, the PRMRP funded 21 awards within the lupus topic area. In FY17 the LRP was established with an appropriation of $5M. The FY18 LRP appropriation is $5M.



FY17 LRP Portfolio Investment by SCS Code

PROGRAM GOALS AND STRATEGY

A hallmark of the LRP is its focus on high-risk, high-reward research that offers the promise of shifting current paradigms to novel avenues of research with the hope of improving treatments and quality of life for those living with lupus. To this end, the LRP is offering two mechanisms in FY18 that focus on innovative and impactful research. Additionally, research submitted to the LRP in FY18 must address at least one of three focus areas.

FY18 AWARD MECHANISMS

CONCEPT AWARD

- Supports highly innovative, untested, potentially ground-breaking concepts in lupus research
- Supports high-risk, high-reward studies that have potential to reveal new avenues of investigation
- Emphasis is on innovation
- Preliminary data is not required

IMPACT AWARD

- Supports full spectrum of research projects or ideas which, if successful, have the potential to make major impact in lupus
- Supports high-risk, high-reward studies that have potential to make significant advancement
- Emphasis is on impact
- Preliminary data is encouraged but not required

FY18 FOCUS AREAS

LUPUS HETEROGENEITY

- Understand lupus disease heterogeneity including, but not limited to, progressive stages of lupus over time, strategies and technologies to subtype patients, understanding lupus disease mechanisms, biopsychosocial studies, personalized medicine, variation in treatment and its effects on patient outcomes, socioeconomic studies, environmental studies, and epidemiological studies.

LUPUS GENETIC COMPONENTS

- Understand how the underlying genetic components and gene-environment interactions of lupus relate to clinical disease characteristics using functional genomic studies.

LUPUS PATHOBIOLOGY

- Determine the pathobiology of lupus disease in target human tissues including, but not limited to, imaging studies, genomics of lupus in particular tissues, and metabolomics.

"Over the 27 years I have lived with lupus, nothing has drastically changed regarding medication options and improving patient quality of life. That is why I am honored to participate in the Lupus Research Program. Having been involved in both the Stakeholders Meeting and Programmatic Panel, I had the opportunity to share my concerns, provide patient insights, and offer consumer suggestions with some of the top researchers and lupus specialists in the country. This groundbreaking program gives patients like me a voice and a bright hope for a cure. Thank you, CDMRP for establishing this desperately needed program!"

Kelli Roseta
MoreThanLupus.com, Stakeholder and Ad-Hoc Programmatic Panel Member

"The Lupus Research Program completes its first year this year, and we received an impressive array of applications, both in number and scientific diversity. As a panel member, it was impressive to see the large turnout, and it reminds us of the large number of unanswered questions in the disease. It was a pleasure to serve on the panel – we all made our best efforts to support the science that will make a difference in lupus. LRP support is critical to move this field forward, and the LRP Program will allow for some top notch studies to proceed that otherwise would not see the light of day."

Timothy Niewold
New York University, FY17-FY18 Programmatic Panel Co-Chair

Military Burn Research Program

VISION

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

MISSION

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

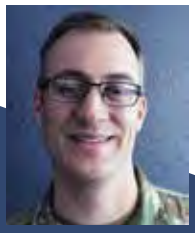
PROGRAM HISTORY

The Military Burn Research Program (MBRP) was initiated in 2011 to address capability gaps for treating combat burn injuries. These gaps were identified by the CCCRP, and they address injuries obtained from the point of injury to treatment at stateside Military Burn Centers. Combat burn injuries are devastating and are often 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] In addition to burns, Service members may also suffer from fractures, amputations, smoke inhalation, and head injuries at the same time. This traumatic assault adds additional burden to the body's innate immune response and, thus, increases the likelihood of infections and organ damage.

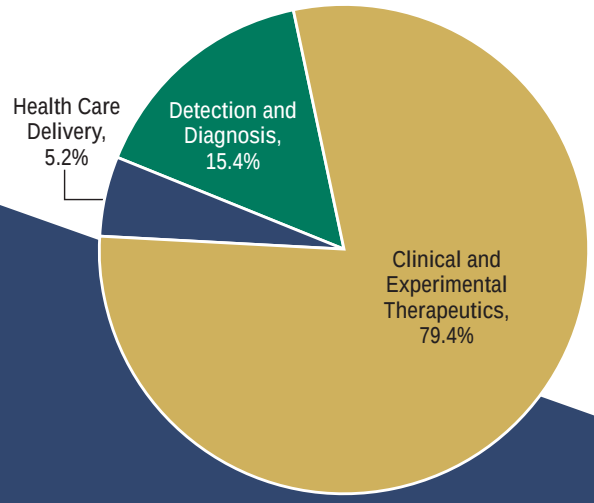
MBRP-funded projects explore innovative approaches to accelerate the translation of advances in knowledge into new standards of care for the treatment of injured Service members, Veterans, and those within the civilian community who sustain burn injuries. The continued efforts, in concert with the program's successes, have resulted in more than $62M in congressional appropriations through FY18.

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



"Research provides an opportunity for an improved reality among burn patients. While relatively rare among the civilian population, the warfighter is disproportionately affected due to explosive devices. A burn from any cause frequently is a life-altering event for the patient. Intensive multidisciplinary care is required early in the course and survivors can often expect years of physical therapy and operative procedures. The combined efforts of medical care team members, scientists, and consumers/patients through the Military Burn Research Program have driven and continue to drive innovation with tangible improvements in patient care."

LTC Jamison Nielsen
FY17 Programmatic Panel Member



FY11–FY17 MBRP Portfolio Investment by SCS Code

Dr. Andriy Batchinsky with the Geneva Foundation and the USAISR, with support from the MBRP developed and demonstrated a novel early intervention for Acute Respiratory Distress Syndrome (ARDS). This was accomplished by utilizing a central venous administration of autologous and allogeneic porcine mesenchymal stem cells in a swine model with thermal burns and smoke inhalation injury. In a 72-hour round-the-clock intensive care unit (ICU) study this new treatment protocol involving repeated applications of stem cells early in the first 48 hours after injury has demonstrated oxygenation benefit, a 48-hour delay in ARDS development, and a reduction in ARDS severity compared to untreated controls with severe smoke inhalation and 40% total body surface area deep burns. These findings could lead to novel treatments to significantly reduce morbidity and mortality due to lung failure.

Dr. Jeremy Pamplin and the team at the USAISR, with support from MBRP developed and validated burn ICU, patient-centric checklists for assessment of patient condition and corresponding treatment priorities according to the Phases of Illness Paradigm at three participating American Burn Association burn centers. Preliminary results demonstrated improvement in team member agreement regarding patient condition and reduced cognitive work associated with identifying patient condition and care priorities. Caregivers perceived improvements in team communication, patient safety, and patient outcomes using these tools. This technology could potentially become a standard clinical tool for the assessment and determination of treatment priorities for burn patients.

Projects Funded Based on FY11-FY17 Topic Areas

MBRP FY11-FY17 Focus Areas	% Funding per Topic Area
Accelerated Wound Healing	27%
Infection and Sepsis	15%
Hypertrophic Scarring	14%
Rehabilitation (Physiology or Outcomes)	11%
Lung Injury	11%
Fluid Resuscitation	8%
Healing Acute Burns	6%
Clinical Impact of Delayed Therapy	6%
Standardization of Burn Care	2%

"In regards to serving as a Consumer Reviewer, I think the biggest thing is when I am sitting in the Peer Review Panel room with over a dozen scientists, many of whom are the smartest people in their fields. As an Army Master Sergeant, I would never have thought that a super genius would want to hear what I have to say and actually ask me questions on how something affects our combat wounded heroes. I think it is our obligation [as Consumer Reviewers] to share what we went through and how we recovered so that future generations of burn Veterans do not endure the difficulties that we did."

MSG Bobby Ehrig (Ret.)
Consumer Reviewer

Multiple Sclerosis Research Program

VISION

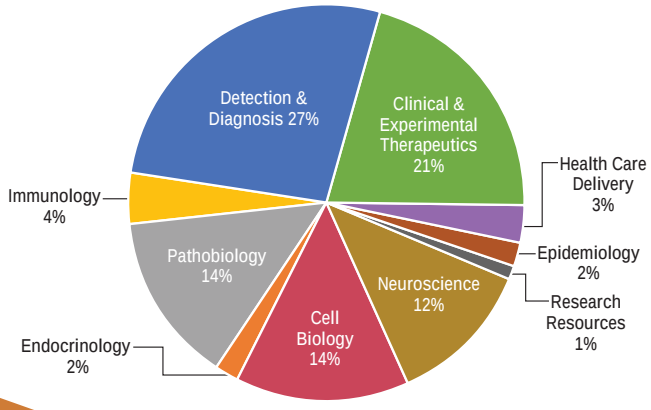
To prevent, cure, reverse, or slow the progression, and lessen the personal and societal impact of multiple sclerosis.

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 degenerative, chronic inflammatory disease of the CNS that leads to cumulative neurologic disability over several years. It is a heterogeneous and unpredictable disease that can manifest in many ways across the patient population with MS. Common manifestations include pain, fatigue, cognitive dysfunction, visual impairment, motor impairment, impaired mobility, loss of bladder control, sexual dysfunction, depression, and anxiety. Although MS affects over 400,000 individuals in the United States and about 2.5M individuals worldwide, its etiology and pathogenesis are largely unknown. 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 40. Currently, there is no cure for MS. In FY09, Congress appropriated $5M for MS research, and the Multiple Sclerosis Research Program (MSRP) was established. Since then, a total of $51.1M has been appropriated to the program, including $6M in FY18.



FY09–FY17 MSRP Portfolio Investment by SCS Code

PROGRAM PORTFOLIO

Through FY17, MSRP funded 91 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.

LINK BETWEEN ALTERATIONS IN THE GUT MICROBIOTA AND MS

Kouichi Ito, PhD, Rutgers-Robert Wood Johnson Medical School

Dr. Ito and his team received an FY11 Idea Award to investigate the effects of gut dysbiosis and age on the development of CNS autoimmunity. They found that in transgenic mice expressing human leukocyte antigen–DR isotype 2a (HLA–DR2a) and T cell receptors specific for myelin peptides isolated from MS patients, the gut biome was overgrown by the bacterial species, *Bacteroides vulgatus*, during adolescence and young adulthood and this resulted in the development of spontaneous experimental autoimmune encephalomyelitis (EAE), an animal equivalent of MS. Dr. Ito and his team further elucidated that EAE results from the decreased expression of forkhead box P3 (*FOXP3*), casitas B-lineage lymphoma b (*CBLB*), and itchy E3 ubiquitin protein ligase homolog (*ITCH*) genes in T cells, which alters the immunological tolerance to myelin basic protein. Additionally, increased intestinal permeability and blood endotoxin levels accompanied this spontaneous EAE, supporting the hypothesis that gut dysbiosis is one of the risk factors associated with the onset of CNS autoimmunity. These findings highlight the importance of the gut microbiota and suggest that gut dysbiosis may play a pathological role in the initiation and progression of MS during adolescence and young adulthood.

Pilot Clinical Trials Underway		
Ellen Mowry, MD, Johns Hopkins University	Intranasal Insulin for Improving Cognitive Function in MS	**Goal:** Evaluate whether insulin is safe and tolerable in people with MS and can improve their cognition: NCT02988401
Kottil Rammohan, MD, University of Miami, Coral Gables	Histaminergic Basis of Central Fatigue in MS - A Novel Therapeutic Approach	**Goal:** Define strategies that will raise histamine levels in the brain to overcome fatigue: NCT03266965
Joseph Finkelstein, MD, PhD, Columbia University Medical Center	Physical Telerehabilitation in Patients with MS with Significant Mobility Impairment	**Goal:** Assess the feasibility and impact of an innovative home-based physical telerehabilitation model in MS patients with significant mobility impairment: NCT03230903
Leigh Charvet, PhD, New York University School of Medicine	Remotely Supervised Transcranial Direct Current Stimulation (RS-tDCS) to Enhance Motor Learning in Progressive MS	**Goal:** Evaluate the efficacy of a remotely supervised platform for in-home delivery of tDCS to enhance hand rehabilitation in individuals living with progressive MS with reduced manual dexterity: NCT03499314

"By the conclusion of my own participation in MSRP I was more hopeful about the future. I saw that the evaluations of the next generation of fundamental MS research are being conducted in a systematic manner by scientists balanced by the direct input of the needs of the MS community. I am confident that the limited MSRP funding is being applied to the most promising avenues of MS research."

Gary Pinder
National Multiple Sclerosis Society
FY17 Consumer Peer Reviewer

Neurofibromatosis Research Program

VISION

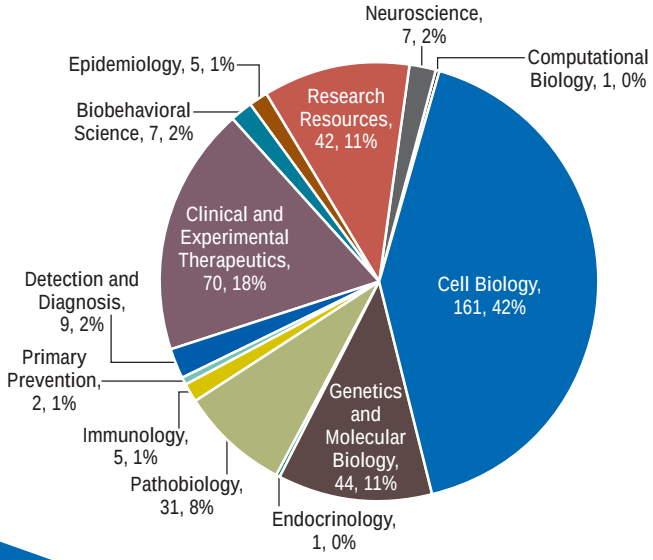
Decrease the clinical impact of neurofibromatosis.

MISSION

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

PROGRAM HISTORY

NFRP was established in FY96 when the efforts of NF advocates led to a congressional appropriation of $8M. Since that time, $332.85M has been appropriated to the program, including $15M in FY18. 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–FY17 NFRP Portfolio Investment by SCS Code

"My experience with the NFRP has been amazing. I, as a Consumer Reviewer, felt respected and more importantly, heard. I truly feel that being part of the NFRP is one of the most important things I have done for my Riley and all those with NF."

Michelle Hirsch Donovan
Consumer Peer Reviewer
Michelle Hirsch Donovan's daughter, Riley Donovan, has been diagnosed with NF

David Gutmann, MD, PhD, Washington University, St. Louis, Missouri

Neurofibromatosis type 1 (NF1), caused by mutations in the NF1 tumor suppressor gene, can manifest in patients in different ways, one of which is the growth of low-grade gliomas of the optic pathway (OPGs). These gliomas are slow growing, heterogeneous, and they develop during childhood, making them difficult to treat with chemotherapy. Dr. David Gutmann received an FY12 IIRA through the NFRP to study the tumor cells, microenvironment of OPGs, and their interactions to discover novel therapeutic targets for treatment. In 2015, his group published a report demonstrating the isolation and characterization of cancer stem cells (SCs) from low-grade gliomas from Nf1+/- mice with somatic Nf1 gene inactivation in their neuroglial progenitor cells. When injected into the brainstems of Nf1+/- mice, cancer SCs were able to form glioma-like lesions. Interestingly, injection of the optic glioma stem cells into athymic mice did not give rise to gliomas, underscoring the importance of the Nf1+/- microenvironment to tumor formation. In their recent publication, Dr. Gutmann's group examined the cell of origin of optic gliomas in two different mouse models, one in which somatic Nf1 mutation occurs in oligodendrocyte precursor cells (OPCs) and another in which neural progenitor/stem cells undergo somatic Nf1 loss. Both sets of mice developed gliomas, but the gliomas derived from the neural progenitor/stem cells developed by 3 months of age, whereas the gliomas derived from the OPCs developed at 6 months of age, suggesting that the time to tumorigenesis may be due to differing cells of origin. Using mouse models with different Nf1 mutations and cells of origin, Dr. Gutmann's group demonstrated that while the optic gliomas in the various mouse models all looked similar with immunohistological analysis, RNA-sequencing of the whole tumor showed distinct molecular signatures. The gene expression pattern observed in the tumor reflected the intercellular interactions within the tumor, not the individual cell types, highlighting the importance of considering the tumor as a whole. The group also determined that neither carboplatin nor rapamycin treatment resulted in significant changes in the tumor signature; however, minocycline treatment, which targets microglia, shifted the gene signature towards the non-tumor tissue signature. Dr. Gutmann's studies under this award have led to greater knowledge of the cellular components and the importance of their interactions in optic glioma development. These findings have laid the groundwork for future studies into potential biomarkers for effectiveness of treatment and prognosis for NF1 patients, pointed to novel targets for optic glioma treatment, and provided mechanistic insights into drug resistance to currently used treatments.

Cristina Fernandez-Valle, PhD, University of Central Florida

Neurofibromatosis type 2 (NF2) is a genetic syndrome caused by the loss of function of the NF2 gene that encodes the Merlin tumor suppressor protein. The loss of Merlin causes Schwann cells (cells that wrap around nerves) to form noncancerous tumors called schwannomas on cranial, spinal, and peripheral nerves. The treatment options for patients with schwannomas is often limited to surgery, which is not ideal, as serious adverse effects such as nerve damage are often associated with the tumor removal. With an FY14 NFRP IIRA, Dr. Fernandez-Valle and her laboratory investigated FDA-approved drugs targeting Src and c-Met to determine if they could be repurposed for schwannoma treatment. When Merlin-deficient mouse Schwann cells were treated singularly with the c-Met inhibitor, cabozantinib, or with one of the Src inhibitors, ponatinib, dasatinib, or saracatinib, they displayed reduced viability. When the cells were treated with a combination therapy of cabozantinib and saracatinib, apoptosis (cell death) was selectively induced in Merlin-deficient Schwann cells but not in wildtype (normal) Schwann cells. The combination treatment also reduced growth of Merlin-deficient mouse Schwann cells in a mouse model by 80% compared to vehicle treatment. In addition, human schwannoma cells with NF2 mutations displayed a 40% decrease in cell viability with the combination treatment when compared to control treatment. The success of these repurposed drugs in inhibiting Merlin-deficient Schwann and schwannoma cell proliferation warrants future studies to further address the possible use of these drugs as effective therapies for NF2 patients. Also, these results indicate that the combined inhibition of Src and c-Met can trigger Schwann cell death, which suggests a vulnerability in schwannomas that could potentially be targeted for the development of much needed NF2 therapies.

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.

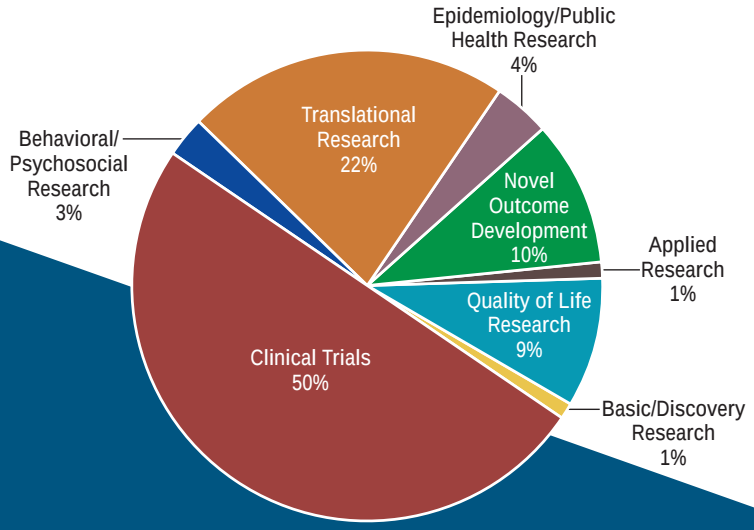
PROGRAM HISTORY

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.

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

"I find the whole experience to be enriching, from reading the proposals to engaging with the medical and academic communities as ideas and proposals are discussed, to how well-organized the overall process is, these panels provide great insights about what the future may hold. I like being a part of that."

Max Ramsey
Consumer Peer Reviewer



FY14-FY17 OPORP Investments
$36,882,240 in 38 Awards

BRIAN HAFNER, PhD

As the recipient of an FY14 Orthotics and Prosthetics Outcomes Research Award, Dr. Brian Hafner and his research team at the University of Washington conducted a randomized crossover study to compare outcomes associated with the use of a modified running-specific foot, termed a "crossover foot" (XF), to a traditional energy-storing foot (ESF). The University of Washington team compared the performance of these two prosthetic feet across different health domains, including metabolic energy cost, endurance, perceived exertion, gait quality, and step activity. The researchers found that, on average, users had slightly lower oxygen consumption in the XF compared to the ESF. Furthermore, study participants reported about 20% less exertion when walking long distances and generally walked with a more even step pattern in the XF. The researchers also measured users' perceived performance while they wore each foot for a month. Users reported that the XF improved their mobility, balance, and function. The XF also reduced users' fatigue and restrictions in activity from the prosthesis. Results of the study collectively indicate that XF and ESF prostheses provide equivalent function for level ground walking, but the XF may offer benefits to users in real-life conditions. Dr. Hafner suggests the XF may provide a unique, "all-in-one" solution for Service members, Veterans, and civilians who wish to engage in a wide range of activities. Dr. Hafner's team next plans to study the relative performance of XF and ESF under more rigorous real-world conditions – such as walking on stairs and inclines, jogging, and carrying loads – in order to inform development of improved XF, including a version for Service members who wish to return to active duty.

DAVID MORGENROTH, MD

Dr. Morgenroth is a physician-scientist who is seeking to improve the mobility of individuals with lower limb amputation by optimizing the process of prescribing prosthetic feet. As the recipient of an FY15 Level 2 Prosthetics Outcomes Research Award, Dr. Morgenroth and his team of co-investigators are studying a patient centered test-drive strategy for prescribing prosthetic feet. They are using a novel, customizable, robotic prosthetic foot that mimics the mechanical properties of commercial prosthetic feet through software control without physically changing feet. This "prosthetic foot emulator" can provide people with leg amputations the opportunity to quickly "test-drive" many prosthetic foot designs within a single test session. In order to give study participants a chance to test-drive feet under a variety of environmental terrains, laboratory testing includes walking on flat ground at different speeds, walking on slopes, and walking up stairs. After laboratory testing, participants wear each of the actual prosthetics for normal activity for 2 weeks and return for re-evaluation in the laboratory. The study will compare users' preference for emulated feet to their preference for use of the actual prosthetic to ensure that the emulation is accurately capturing the feeling of wearing and using the foot. By allowing patients a chance to offer valuable experiential feedback during the prescription process, this study has the potential to provide meaningful benefit to clinicians, as well as to Service members and Veterans with leg amputations. Patients who are engaged in medical decision making are known to have better outcomes; allowing patients to participate and offer experiential feedback during the prosthetic foot prescription process, using either the emulator or a brief trial of commercial prosthetic feet, has great potential to enable increased patient satisfaction, walking ability, and achievement of functional goals.

"The OPORP goes beyond simply advancing orthotic and prosthetic outcomes research. Our clinically-focused Programmatic Panel employs a "function first" approach to carefully evaluate the needs of individuals with extremity trauma and amputation, with the ultimate goal of returning these individuals to their desired lifestyle."

Rachel Evans

Civilian Consultant, FY15-FY18 Programmatic Panel Member

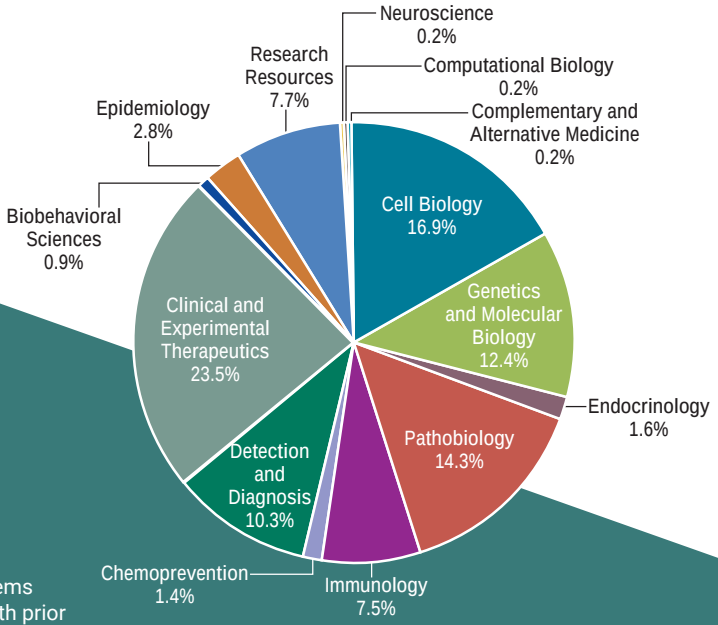
Ovarian Cancer Research Program

VISION
To eliminate ovarian cancer.

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

PROGRAM HISTORY
The DOD OCRP was established in 1997 to define and address the critical research gaps facing the ovarian cancer community. The appropriation for OCRP for FY18 is $20M. With $316.5M in Congressional appropriations through FY18, 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. To date, the OCRP has funded 427 research awards, resulting in over 1,583 peer-reviewed publications and 103 patent applications.

PROGRAM PORTFOLIO: FUNDING RESEARCH FROM BENCH TO BEDSIDE
The OCRP designed an investment strategy that emphasizes high-impact translational research, innovation, and development for talented young investigators who are committed to studying this disease. The OCRP investment strategy portfolio shows the percentage of awards funded in each research area. There is widespread funding across scientific areas.



FY97-FY17 OCRP Portfolio Investment by SCS Code

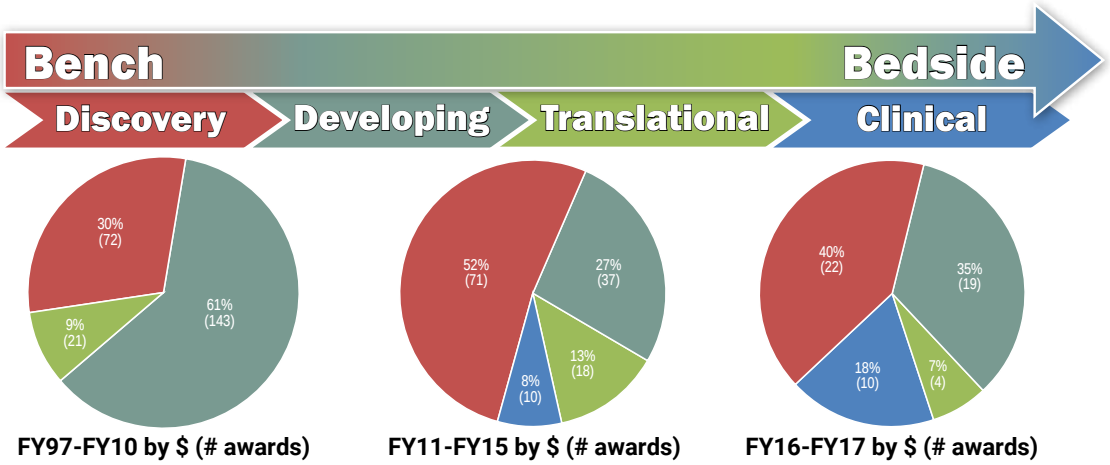
HIGH-IMPACT ADVANCES SUPPORTED BY THE OCRP

New Research Tools
- Animal models of ovarian cancer
- Shared biorepository of clinical data and biospecimens
- OPHID/I2D: An online database of protein interactions

Prevention, Detection, and Diagnosis
- Genetic testing guidelines in the US and Australia
- Salpingectomy as a less invasive alternative surgery
- Falloposcope system to identify ovarian cancer
- Adapting pap smears to detect ovarian cancer

Treatment
- Targeting tumor vasculature to eliminate ovarian cancer cells
- Junctional opener 1 to make treatment more effective
- Exercise to reduce the effects of chemo-induced memory problems
- Accelerated FDA approval for rucaparib treatment in patients with prior chemotherapies and recurrences

The OCRP funds research across the bench-to-bedside continuum as shown here. In recent years, there has been increasing emphasis on high-impact clinical research that has immediate benefits to the ovarian cancer patient.



OVARIAN CANCER ACADEMY: EMPOWERING A DETERMINATION TO DEFEAT OVARIAN CANCER

The Ovarian Cancer Academy is designed do help establish the next generation of dedicated ovarian cancer researchers. See page 23 for more information about the Academy.

HIGH-IMPACT RESEARCH IN THE ACADEMY

Rugang Zhang, PhD, The Wistar Institute — FY09 Academy Member

Dr. Zhang explored the role of cell senescence and canonical Wnt signaling in epithelial ovarian cancer with the hopes of developing novel therapeutic strategies for treating the devastating disease. He demonstrated that the loss of Wnt5a contributed to epithelial ovarian cancer development by enabling the cancer cells to overcome senescence. He verified that Wnt5a was expressed at lower levels in primary epithelial ovarian cancers, and that the loss of Wnt5a correlates with a high cell proliferation index. A lower level of Wnt5a was also shown to be a poor prognosis biomarker in epithelial ovarian cancer. These results suggest a mechanism that could be targeted to drive malignant cells to undergo senescence and stop cancer cell growth. A patent is pending, and subsequent funding has been received from OCRP to continue research into other therapeutic strategies for ovarian cancer.

Geeta Mehta, PhD, University of Michigan — FY12 Academy Member

A major gap in designing novel therapies is the different reaction an anticancer drug displays in a 2-dimensional cell culture environment versus that observed in patients. Dr. Mehta developed a 384-hanging drop array of 3-dimensional spheroids to help bridge that gap. The spheroids contain ovarian cancer stem cells derived from human patient samples that grow as if inside the body. This allows for multiple therapies to be tested simultaneously against a patient's cells. This technology is an important step toward personalized medicine that will help deliver more precise therapies, resulting in improved care for ovarian cancer patients. Multiple papers have been published, and subsequent funding was received from the OCRP to continue the project; to date, small molecule drug N7-73 showed remarkable potency in chemoresistant ovarian cancer spheroids.

Erinn Rankin, PhD, Stanford University — FY14 Academy Member

Dr. Rankin hopes to improve the survival of patients suffering from this deadly disease by identifying new therapies targeting its microenvironment. Hypoxia, or low oxygen availability, is a key molecular factor within the tumor microenvironment that promotes metastatic progression. Dr. Rankin generated a novel mouse model to investigate the role of the hypoxia inducible transcription factors (HIFs) in cells of the tumor microenvironment, such as regulatory T cells. Currently, HIF inhibitors are in the early stages of clinical development, suggesting the feasibility of these agents in future clinical trials in ovarian cancer patients. Dr. Rankin has also received subsequent OCRP funding.

"The OCRP Academy Award was instrumental in launching my independent ovarian cancer research program. The award was not only a catalyzer of my own independent career development but also served as an amplifier for training the next generation of dedicated ovarian cancer researchers." "The impact of the award on ovarian cancer is certainly long-lasting and far-reaching."

Rugang Zhang
The Wistar Institute

Parkinson's Research Program

VISION

To stop Parkinson's disease by funding research through a partnership of scientists and consumers.

MISSION

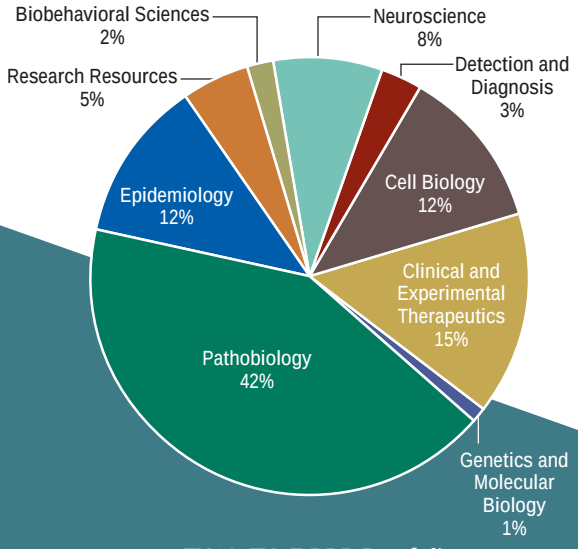
Support research to understand, prevent, diagnose, and treat Parkinson's disease in patients, including Service members and Veterans.

PROGRAM HISTORY

Parkinson's disease (PD) is a degenerative movement disorder of the CNS resulting from a loss of neurons in a region of the brain called the substantia nigra. These neurons produce dopamine, a neurotransmitter important for motor control; however, as PD progresses, the death of dopaminergic neurons results in reduced dopamine levels and impairment of motor control. The Parkinson's Research Program (PRP; funded under the Neurotoxin Exposure Treatment Parkinson's Research [NETPR] appropriation) was initiated in FY97 to provide support for research of exceptional scientific merit leading to an understanding of the cause, prevention, and treatment for the loss of dopaminergic neurons in the substantia nigra that result in PD. Projects examine neurodegenerative mechanisms and compensatory effects that compromise motor, autonomic, and cognitive systems that are characteristic alterations in PD patients and also present performance and health risks for military personnel. From FY97 through FY17, approximately $420.75M has been appropriated by Congress for PD research. The FY18 appropriation is $16M. The PRP challenges the scientific community to develop the most impactful research that will advance the understanding of PD, with the ultimate goal of ending this disease.

PROGRAM PORTFOLIO

The PRP has funded 234 awards through FY17 to support innovative research with the potential to yield new avenues of investigation and make a major impact in the understanding, prevention, diagnosis, and treatment of PD.



FY10-FY17 PRP Portfolio Investment by SCS Code

IDENTIFICATION OF PREMOTOR PARKINSON DISEASE

Alberto Ascherio, MD, DrPH, Harvard University

Identifying PD in the premotor phase before substantial neuronal loss could improve outcomes from potential neuroprotective therapies. With the support from an FY13 BAA award, Dr. Ascherio initiated a large longitudinal investigation to identify individuals who are at high risk of PD or in the premotor phase of PD by estimating the prevalence of probable rapid eye movement sleep behavior disorder (pRBD), constipation, and hyposmia and their association with PD in a cohort of 18,000 men. Dr. Ascherio demonstrated that experiencing all three symptoms was distinctly rare among otherwise apparently healthy individuals but was quite common among individuals with PD. He also demonstrated a probable association between these symptoms and alpha-synuclein aggregation at different anatomical locations. The odds of PD increased exponentially and were 167-fold higher in men with all three symptoms compared to those with none. These initial findings demonstrate the feasibility of a large-scale screening program that includes pre-screening for constipation and pRBD and subsequent administration of smell testing to identify individuals who are likely to be at high risk of PD. Dr. Ascherio is examining other potential signs of prodromal PD to improve the ability to screen for early symptoms or signs of PD neurodegeneration before clinical diagnosis is possible.

GENETIC ASSOCIATIONS IN PARKINSON'S DISEASE

Andrew Singleton, PhD, National Institute on Aging, NIH

Much progress has been made in the discovery of genetic risk traits for PD, which is the second most common neurodegenerative disorder.[1] In advancement of PD research and through the support of an FY15 BAA award, Dr. Singleton and his team of researchers carried out a genome-wide association study of PD cases and controls to (1) refine the list of known genetic variants that are associated with the risk of PD; (2) identify novel variants associated with risk of the disease; and (3) determine which variants are associated with the disease's progression.

In the first stage, a discovery meta-analysis of 9,830 single nucleotide polymorphisms was conducted using data from the Web-Based Study of Parkinson's Disease and PDGene study. Thirty-five traits were carried on to the next stage of replication meta-analysis using NeuroX cases and controls, which resulted in identification of 17 new traits for further downstream analyses. It was also discovered that several of the newly identified traits played a role in lysosomal biology and autophagy (processes that are implicated in PD by different variants). Dr. Singleton's analysis is the leading, largest meta-analysis known, and the results indicate opportunities for prioritizing functional studies of PD causal genes, optimizing therapeutic viable points, and furthering new discovery. The dataset generated also provides a rich resource for the public and the research/scientific community.

Publication:

Chang D, Nalls M, Hallsgrimdottir I, et al. 2017. A Meta-Analysis of Genome-Wide Association Studies Identifies 17 New Parkinson's Disease Risk Loci. *Nat Genet*. 49:10.

Reference:

1.Corti O, et al. 2011. *What Genetics Tells Us About the Causes and Mechanisms of Parkinson's Disease*. *Physiol. Rev*. 91:1161–1218.

"The Parkinson's Research Program plays a critical role in the shared goal to end Parkinson's disease. The program has helped fund ground-breaking scientific discovery and lead the charge to find environmental exposures that increase the risk of Parkinson's disease. As the daughter of an Air Force Veteran and a physician to thousands of patients suffering from Parkinson's disease, I am deeply privileged to be part of this important program."

Kathleen Poston

Stanford School of Medicine, Programmatic Panel member

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

Dedicated to (1) understanding the association between traumatic brain injury and Alzheimer's disease/Alzheimer's disease related dementias and (2) reducing the burden on affected individuals and caregivers, especially in the military and Veteran communities.

PROGRAM HISTORY

Military personnel and other individuals living with TBI face an increased risk for developing several long-term health problems. These include dementia, aggression, memory loss, depression, and symptoms similar to those of other neurological diseases. The PRARP (formerly the Militarily Relevant Peer Reviewed Alzheimer's Disease Research Program) was initiated in FY11 to address the long-term consequences of TBI as they pertain to AD and ADRD. Consistent with the PRARP's mission, the PRARP faces six overarching challenges.

- Paucity of Research Resources
- Paucity of Clinical Studies
- Diagnostic Technologies, Tests, Biomarkers, or Devices
- Quality of Life
- Caregiver Support
- Epidemiology

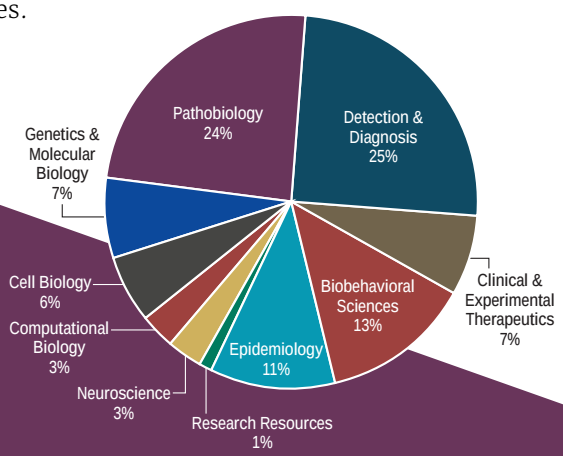
In order to answer these overarching challenges, the PRARP has identified seven scientific focus areas that support innovative and systematic research:

- Mechanisms of Pathogenesis
- Biomarkers
- Quality of Life
- Caregiver Support
- Epidemiological Research
- Novel Target Identification
- Nonpharmacological Interventions

Between FY11 and FY17, the program administered $93M in funding across 90 awards that are intended to address at least one of the PRARP's overarching challenges.

"The PRARP is the only program focused on the relationship of military risk factors to the development of dementia and improvements in quality of life for those affected as well as their caregivers. These resources promote collaborations between researchers from dementia and traumatic brain injury across a variety of disciplines. The program has an impressive track record of scientific discovery that has opened windows for all dementia research and is fortunate to have the collaboration of key federal agencies and the Alzheimer's Association."

Michael Jaffee
FY18 Programmatic Panel Chair



FY11–FY17 PRARP Portfolio Investment by SCS Code

THE IMPACT OF PERK ON POST-TRAUMATIC TAUOPATHY IN ALZHEIMER'S DISEASE

Jose Abisambra, PhD, University of Kentucky

Novel biomarkers can start in a variety of places, perhaps as a newly discovered molecular pathway that requires more characterization as a potential molecular target. The biology of Tau, the protein found in "tangles" within brains showing signs of either injury or neurodegenerative disease, still remains largely a mystery in terms of how Tau exerts its deleterious effects. Tau is a putative fulcrum between brain injuries and long-term diseases such as AD. Dr. Abisambra was awarded an FY14 Convergence Sciences Research Award to examine whether TBI activates the protein kinase R-like endoplasmic reticulum kinase (PERK). He hypothesizes that PERK activation may be a marker of cellular stress that may ultimately influence how Tau can negatively impact the brain after TBI. As a result of this study, Dr. Abisambra has shown early and sustained activation of PERK after TBI in a model animal system. Furthermore, Dr. Abisambra's study has shown that he can modulate the effects of PERK activation, since this study has identified some of the other signaling molecules involved in the PERK response. He has also identified that neurons are the cells that are most affected by PERK activation. These signaling molecules respond to small molecule inhibitors, paving the way for potential preclinical research. Further work is needed to understand how this mechanistic research can be extended to Tau pathology. In addition to the mechanistic work, this study will also couple those findings with state-of-the-art MRI, which will accelerate future research.

USING MULTIMODAL IMAGING TO EXAMINE THE NEURAL MECHANISMS OF AN INTEGRATIVE EXERCISE PROGRAM FOR INDIVIDUALS WITH DEMENTIA

Linda Chao, PhD, Northern California Institute for Research and Education

Non-pharmacological interventions to either slow or stabilize cognitive decline represent novel strategies to improve the daily lives of individuals living with the long-term symptoms of TBI or AD/ADRD. Interventions such as these could be used at home and perhaps alongside a caregiver with no side effects associated with medications. Exercise is one the most promising approaches; however, ways to measure the benefit and optimize the regimen for each individual are lacking. Dr. Linda Chao has proposed examining an exercise regimen called Preventing Loss of Independence through Exercise (PLIÉ), which is performed in a group setting. PLIÉ integrates elements from traditional Western approaches with various mind-body techniques to: (1) train procedural memory, which remains intact in individuals with AD/ADRD, for basic functional movements that are important for maintaining independence (e.g., sit-to-stand); (2) increase mindful body awareness; and (3) facilitate social connections. Preliminary data showed that an 18-week course of PLIÉ had positive benefits, including reducing the caregiver burden. Dr. Chao, with support from a PRARP FY16 Quality of Life Research Award, is taking these preliminary findings one step further by coupling a new study of PLIÉ with state-of-the-art neuroimaging. It is hoped that the neuroimaging results will not only demonstrate how well the PLIÉ intervention works, but also characterize the individuals who will benefit the most from this type of intervention. While some individuals may benefit more than others, those who show lesser benefit will be also studied closely. Study outcomes for these individuals may lead to a modified intervention based on PLIÉ that will benefit them as well.

"As a former caregiver for two veterans with an Alzheimer's diagnosis, I have seen the impact on both the person living with the disease and the caregiver. Research is the key to finding effective methods of prevention and new treatments that can reduce or eliminate the effects of Alzheimer's and other dementias. The information and knowledge derived from PRARP-supported research, while focused on military personnel and veterans, can be applicable to other populations affected by Alzheimer's and related dementias. The Alzheimer's Association is proud to collaborate with the PRARP."

Lucien Richardson
Alzheimer's Association

Peer Reviewed Cancer Research Program

VISION

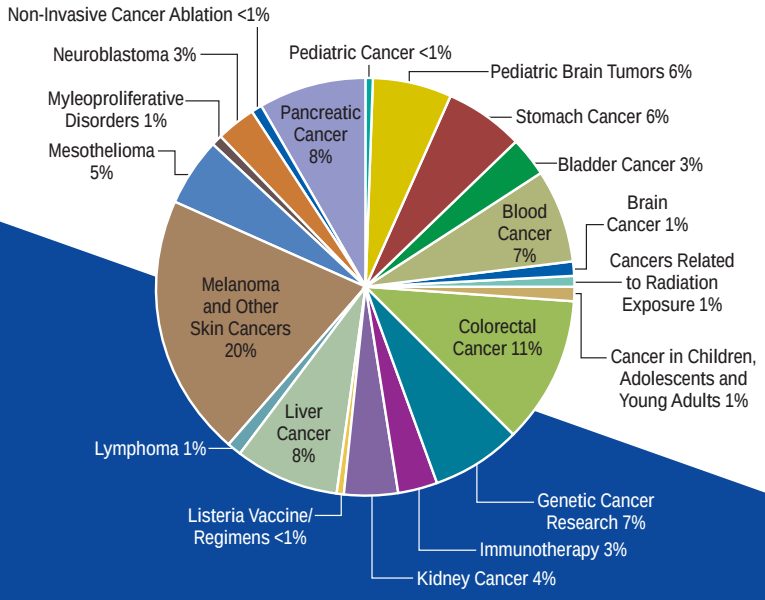
To advance mission readiness of US military members affected by cancer and to improve quality of life by decreasing the burden of cancer on Service members, their families, and the American public.

MISSION

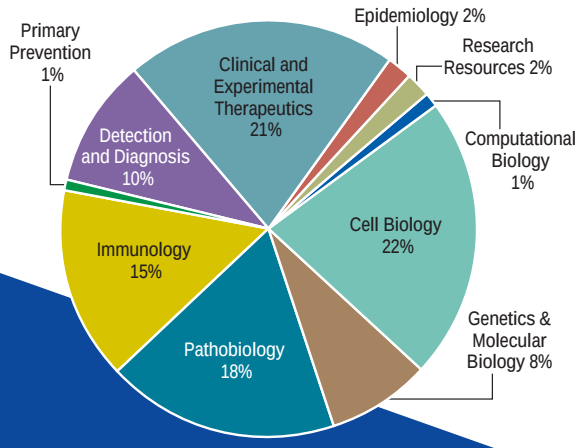
To successfully promote high-impact research for cancer prevention, detection, treatment, and survivorship.

PROGRAM HISTORY

Since FY09, Congress has appropriated $339.8M to the Peer Review Cancer Research Program (PRCRP), which in turn has invested in cancer research covering over 20 topic areas. The program employs a variety of funding mechanisms to address two military relevant focus areas. First, PRCRP funds research into cancers that can develop due to exposures related to military service and deployment. Second, the program aims to address knowledge gaps in cancer care that may affect mission-readiness and the health of all military beneficiaries. PRCRP-funded investigators are performing high-impact, cutting-edge research to advance the knowledge of cancer prevention, detection, treatment, and survivorship for service members and their families, veterans, and the American public.



FY09-FY17 PRCRP Research Investment by Topic Area (% Dollars)



FY09-FY17 PRCRP Portfolio Investment by SCS Code*

** FY17 awards were under negotiation at the time of analysis and so the dollars used for FY17 were not the final budget amounts and are subject to change.*

PRCRP Funded Research Through the Cancer Care Spectrum

Biology/Etiology

Developing a New Therapeutic for Chronic Lymphocytic Leukemia (CLL); *Rosa Lapalombella, PhD, Ohio State University;* ***Topic Area: Blood Cancer***

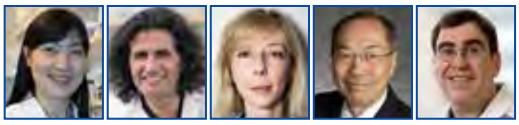
With an FY13 Career Development Award, Dr. Lapalombella discovered that the nuclear export protein, XPO1, is overexpressed in CLL, and that inhibition of XPO1 has therapeutic potential. Results from this award informed the development of a clinical trial using an XPO1 inhibitor called selinexor for treatment of CLL and non-Hodgkin lymphoma.

Prevention

New Sunscreen for Preventing UV-Induced Skin Cancer; *Vijay Krishna, PhD, Cleveland Clinic Foundation;* ***Topic Area: Melanoma and Other Skin Cancers***

Dr. Krishna, supported by an FY14 Idea Award with Special Focus, designed a new, long-lasting sunscreen containing a single, multifunctional active ingredient, polyhydroxy fullerene (PHF), to prevent skin cancers. Animal studies have shown that topical application of PHF protects skin from ultraviolet (UV) damage and prevents sunburn. The results from this study provide data for the development of clinical trials to test for safety and efficacy.

Diagnosis/Detection



Identifying Biomarkers for the Early Detection of Mesothelioma; *Haining Yang, PhD, Michele Carbone, MD, PhD, University of Hawaii; Justyna Fert-Bober, PhD, Cedars-Sinai Medical Center; Tak Mak, PhD, University Health Network, Toronto; Harvey Pass, MD, New York University School of Medicine;* ***Topic Area: Mesothelioma***

Funded by an FY15 Translational Team Science Award, these investigators aim to develop a blood test that can detect mesothelioma in its earliest stages. They plan to focus on an inflammatory protein, HMGB1, which is present in the serum of asbestos-exposed individuals. The identification of a biomarker for mesothelioma would potentially improve detection and treatment outcomes for these patients.

Prognosis

Agent Orange Exposure and Bladder Cancer; *Stephen Williams, MD, University of Texas Medical Branch;* ***Topic Area: Bladder Cancer***

Dr. Williams, funded by an FY16 Career Development Award, will utilize data from the VA Health System to investigate whether Agent Orange exposure during the Vietnam War is correlated with the development of bladder cancer. The results from this study will potentially identify novel risk factors for the development of bladder cancer in the US Veteran population.

Tumor Slice Culture: A New Avatar in Personalized Oncology; *Raymond Yeung, MD, Qiang Tian, MD, PhD, Venu Pillarisetty, MD, University of Washington;* ***Topic Area: Colorectal Cancer***

The investigators, funded by an FY15 Translational Team Science Award, are developing a method to test responses to various chemo- and immuno-therapeutics using colon cancer liver metastasis biopsy samples. This work will advance the field of personalized medicine, with the hope of developing individualized treatment strategies for cancer patients.

Treatment

Mechanisms of Resistance to Immunotherapy in Head and Neck Cancer; *Laura Conforti, PhD, Trisha Wise-Draper, MD, PhD, Edith Janssen, PhD, University of Cincinnati;* ***Topic Area: Immunotherapy***

This study, supported by an FY16 Translational Team Science Award, will focus on why some head and neck cancer patients do not respond to immunotherapy. The investigators are utilizing a clinical trial and animal studies to investigate whether proteins that regulate calcium and potassium signaling in immune cells play a role in anti-programmed cell death protein 1 (PD1) resistance. The results from this study will fill knowledge gaps regarding the molecular mechanisms of cellular resistance to immunotherapy.

A New Model for Understanding Medulloblastoma Development in Children; *Mingyao Ying, PhD, Kennedy Krieger Institute;* ***Topic Area: Pediatric Brain Tumor***

With an FY13 Career Development Award, Dr. Ying established a new model for medulloblastoma using neural cells derived from human-induced pluripotent SCs. This new model, driven by the MYC oncogene, will aid in the identification of new therapeutic targets for treating this aggressive pediatric cancer.

Survivorship

Overcoming Resistance to Trastuzumab in HER2+ Gastric Cancer; *Yelena Janjigian, MD, Sohail Tavazoie, MD, PhD, Jason Lewis, PhD, Memorial Sloan-Kettering Cancer Center;* ***Topic Area: Stomach Cancer***

Trastuzumab, a HER2 inhibitor, is the standard of care for HER2+ gastric cancer, yet most patients eventually develop resistance. With an FY15 Translational Team Science Award, Drs. Janjigian, Tavazoie, and Lewis are investigating the mechanism of trastuzumab resistance and the clinical efficacy of a new HER2 inhibitor, afatinib. The results of this study will inform future therapeutic strategies for HER2+ gastric cancer patients.

Peer Reviewed Medical Research Program

VISION

Improve the health and well-being of all military Service members, Veterans, and beneficiaries.

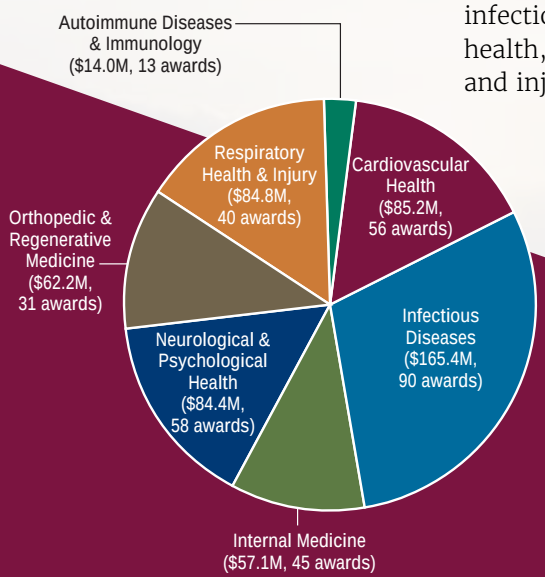
MISSION

Encourage, identify and select military health-related research of exceptional scientific merit.

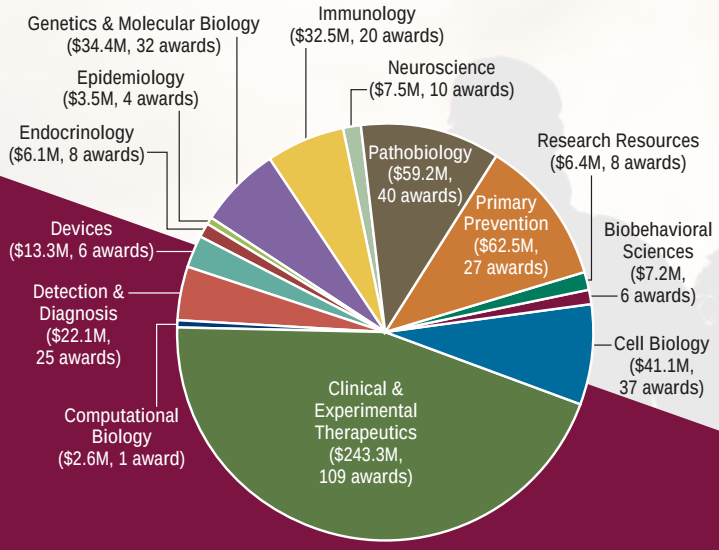
PROGRAM HISTORY

Since 1999, PRMRP has supported research with the underlying goal of enhancing the health and well-being of military Service members, Veterans, retirees, and their family members. Through FY17, Congress has appropriated $1.67B to the program, which has supported more than 1,150 research awards in 134 different Congressionally-directed topic areas. The FY18 Congressional appropriation is $330M to solicit research applications in 52 topic areas.

Research supported by the PRMRP to address near-term military needs continues a long tradition of military medical research 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 cardiovascular health, autoimmune diseases and immunology, infectious diseases, internal medicine, neurological and psychological health, orthopedic and regenerative medicine, and respiratory health and injury.



FY16-FY17 PRMRP Portfolio by Buckets, Wedges % Total Funding



FY16-FY17 PRMRP Portfolio Investment by SCS Code

Autoimmune Diseases & Immunology

Arthritis	FY17 & FY18
Guillain-Barré Syndrome	FY17 & FY18
Hereditary Angioedema	FY17 & FY18
Immunomonitoring of Intestinal Transplants	FY17 & FY18
Inflammatory Bowel Diseases	FY17 & FY18
Rheumatoid Arthritis	FY17 & FY18
Scleroderma	FY17 & FY18

Páraic Ó Cuív, University of Queensland

Award Mechanism: Discovery Award

Dr. Cuív is developing genetic-based approaches to discover novel, natural bioactives isolated from the healthy gut microbiome that can suppress nuclear factor-kappa b (NF-κB). He will test the ability of the bioactive factors to suppress inflammation in a preclinical Crohn's disease (CD) model, with the ultimate goal of developing new, improved therapeutics for CD.

Cardiovascular Health

Cardiomyopathy	FY18
Congenital Heart Disease	FY17 & FY18
Diabetes	FY17 & FY18
Vascular Malformations	FY17 & FY18
Women's Heart Disease	FY17 & FY18

Christopher Breuer, Research Institute at Nationwide Children's Hospital

Award Mechanism: Technology/Therapeutic Development Award

Dr. Breuer is constructing a tissue engineered vascular graft composed of patient-derived bone marrow mononuclear cells seeded onto a biodegradable tubular scaffold. This vascular graft has the capacity to grow as the patient matures and would improve outcomes for children undergoing congenital heart surgery by preventing the need for reoperation.

Infectious Diseases

Antimicrobial Resistance	FY17 & FY18
Diarrheal Diseases	FY17
Emerging Infectious Diseases	FY17 & FY18
Hepatitis B and C	FY17 & FY18
Influenza	FY17
Malaria	FY17 & FY18
Pathogen-Inactivated Dried Cryoprecipitate	FY17
Pathogen-Inactivated Blood Products	FY18
Tuberculosis	FY17 & FY18
Vaccine Development for Infectious Diseases	FY17 & FY18

Pamuk Bilsel, FluGen, Inc.

Award Mechanism: Clinical Trial Award

Dr. Bilsel is developing a novel influenza vaccine designed to generate broad and durable immune protection over multiple influenza seasons. PRMRP is supporting Phase II clinical testing of this novel universal vaccine, which, if successful, will protect against seasonal strain changes and viral shifts that could result in influenza pandemics.

Internal Medicine

Early Trauma Thermal Regulation	FY17
Eating Disorders	FY17 & FY18
Endometriosis	FY18
Epidermolysis Bullosa	FY17 & FY18
Focal Segmental Glomerulosclerosis	FY17 & FY18
Integrative Medicine	FY17
Interstitial Cystitis	FY17 & FY18
Mitochondrial Disease	FY17 & FY18
Nutrition Optimization	FY18
Pancreatitis	FY17 & FY18
Polycystic Kidney Disease	FY17
Sustained-Release Drug Delivery	FY17 & FY18

Todd Kilbaugh, Children's Hospital, Philadelphia

Award Mechanism: Technology/Therapeutic Development Award

Dr. Kilbaugh is developing a therapy for mitochondrial disease caused by mitochondrial complex I dysfunction by identifying a cell permeable succinate pro-drug that bypasses complex I by providing an alternative energy source for mitochondrial complex II. Complex I is the most commonly affected protein complex in mitochondrial disease, and there are currently no approved therapies for treatment.

Neurological & Psychological Health

Cerebellar Ataxia	FY18
Chronic Migraine & Post-Traumatic Headache	FY17 & FY18
Chronic Pain Management	FY18
Dystonia	FY17 & FY18
Fragile X	FY17 & FY18
Frontotemporal Degeneration	FY18
Hydrocephalus	FY17 & FY18
Non-Opioid Pain Management	FY17 & FY18
Rett Syndrome	FY17 & FY18
Sleep Disorders	FY17 & FY18
Spinal Muscular Atrophy	FY17 & FY18
Tinnitus	FY17 & FY18

Lee Swem, Achaogen, Inc.

Award Mechanism: Discovery Award

Dr. Swem and team are developing a non-opioid pain therapy to block NaV1.7, a sodium selective voltage-gated ion channel required for the initial depolarization of an action potential and a key component in pain perception. The antibody therapy they are developing will be highly selective and specific for inhibiting NaV1.7, providing a safe, non-addictive pain treatment option.

Daniel Taylor, University of North Texas, Denton

Award Mechanism: Technology/Therapeutic Development Award

Dr. Taylor aims to develop a user-friendly, web-based provider training course for cognitive behavior therapy-based treatment for insomnia (CBT-IWeb), which has been shown to be one of the best available treatments for this sleep disorder. CBT-IWeb would overcome the challenge of limited training opportunities, and would provide an invaluable resource to an unmet military need to improve Service member psychosocial function and overall health.

Orthopedic & Regenerative Medicine

Musculoskeletal Disorders	FY17 & FY18
Myotonic Dystrophy	FY18
Nanomaterials for Bone Regeneration	FY17
Post-Traumatic Osteoarthritis	FY17 & FY18
Pressure Ulcers	FY18
Tissue Regeneration	FY18

Brian Ilfeld, University of California, San Diego

Award Mechanism: Clinical Trial Award

Dr. Ilfeld will be conducting a multi-site clinical trial of cryoanalgesia as a safe, non-addictive, prolonged treatment for phantom limb pain in individuals with extremity amputation. A large portion of amputees develop this chronic, intractable pain which is perceived as being from the missing limb, and cryoanalgesia has the potential to become the first reliable, definitive treatment.

Respiratory Health & Injury

Acute Lung Injury	FY17 & FY18
Burn Pit Exposure	FY17 & FY18
Constrictive Bronchiolitis	FY17 & FY18
Lung Injury	FY18
Metals Toxicology	FY17 & FY18
Pulmonary Fibrosis	FY17 & FY18
Respiratory Health	FY17 & FY18

Michael Matthay, University of California, San Francisco

Award Mechanism: Clinical Trial Award

Dr. Matthay is conducting a multi-site, Phase IIb clinical trial to test the efficacy and safety of intravenously delivered allogeneic bone marrow-derived human mesenchymal SCs for patients that develop ARDS following major trauma. The therapy could have a major impact on treatment of ARDS, a life threatening condition that currently causes significant morbidity and mortality in both military and civilian trauma populations.

1999

Portfolio: Neuro/Psych Health
Greg Belenky, Walter Reed Army Institute of Research (WRAIR)
Product: Sleep Watch
Award Mechanism: IIRA
Dr. Belenky created a wrist-watch device that measures movement while awake, integrated with a mathematical model to predict performance on the basis of prior sleep in order to predict cognitive performance potential and provide specific recommendations for optimizing sleep and performance during combat and operational deployments.

2002

Portfolio: Respiratory Health/Injury
K. Sree Kumar, Armed Forces Radiobiology Research Institute (AFRRI)
Product: Ex-RAD (Radiation Countermeasure)
Award Mechanism: IIRA
Dr. Kumar conducted preclinical studies on recilisib (Ex-RAD), a medical countermeasure for radiation exposure developed by Onconova Therapeutics, Inc., which led to an IND Exemption from the FDA and multiple Phase I clinical trials.

Portfolio: Infectious Disease
Marcus Horwitz, University of California, Los Angeles
Product: Single Platform Vaccine
Award Mechanism: IIRA
Dr. Horwitz developed a novel tularemia vaccine against aerosolized *F. tularensis* that later led to the development of a single platform vaccine against four Tier 1 bioterrorism agents (tularemia, anthrax, plague and melioidosis), greatly simplifying the vaccination protocol and acceptability of the vaccines.

2003

Portfolio: Infectious Disease
Dr. Stephen Savarino, Naval Medical Research Center/ Henry M. Jackson Foundation
Product: Bovine Milk Immunoglobulin Supplement to Prevent Traveler's Diarrhea
Award Mechanism: New Program Project
Dr. Savarino showed that orally administered bovine milk immunoglobulin collected from cows immunized with enterotoxigenic *E. coli* (ETEC) antigens provides protection against traveler's diarrhea. The product has since been modified to include an additional strain of ETEC, and is being tested as a dietary supplement in an ongoing clinical trial.

2004

Portfolio: Ortho/Regen Med
Ronald Triolo, Case Western Reserve University
Product: Hybrid Neuroprosthesis
Award Mechanism: IIRA
Dr. Triolo developed a prototype hybrid neuromechanical gait assist system that combines electrical stimulation of paralyzed muscles with a controllable hydraulic exoskeleton and demonstrated the system's successful ability to assist individuals with lower extremity motor deficits to perform a variety of activities such as standing, walking, and descending stairs.

2005

Portfolio: Ortho/Regen Med
Roy Bloebaum, Western Institute for Biomedical Research
Product: Percutaneous Osseointegrated Prosthesis
Award Mechanism: Advanced Technology/ Therapeutic Development Award
Dr. Bloebaum developed a percutaneous osseointegrated prosthesis that allows direct skeletal attachment of prostheses to amputated limbs and demonstrated loadbearing ability and lack of infection in a preclinical amputation model, leading to an ongoing Phase I clinical trial.

Portfolio: Infectious Disease
Ai Lin, WRAIR
Product: Novel Class of Anti Malarials
Award Mechanism: Advanced Technology
Early studies conducted by Dr. Lin supported by PRMRP led to development of triazines, a novel class of antimalarial drugs soon to enter clinical phase studies.

2006

Portfolio: Internal Medicine
Dr. Laurence Cooper, MD Anderson Cancer Center
Product: T cell Immunotherapy Method
Award Mechanism: Advanced Technology
Dr. Cooper developed a method for genetically modifying T cells to eradicate malignant B-cells during haploidentical hematopoietic progenitor-cell transplant to treat leukemia and lymphoma, circumventing the need for HLA-identical donors and reducing the risk of graft-versus-host disease.

Portfolio: Neuro/Psych Health
Ronald Hayes, Banyan Biomarkers, Inc.
Product: Banyan Brain Trauma Indicator
Award Mechanism: Existing Program Project
Dr. Hayes and Banyan Biomarkers, Inc. identified two protein biomarkers which can be detected in the blood within 12 hours of a mTBI, which led to the development of the first FDA-approved blood test to evaluate mTBI. The test is expected to dramatically reduce the number of CT scans performed on patients with suspected mTBI.

2008

Portfolio: Ortho/Regen Med
Wolfgang Fink, California Institute of Technology
Product: Ceeable Visual Field Analyzer
Award Mechanism: Advanced Technology/Therapeutic Development Award
Dr. Fink adapted a non-invasive visual performance assessment system that measures 3D visual field defects to be Web-based and accessible worldwide for early detection and treatment of eye diseases and injuries even in austere or remote environments.

2010

Portfolio: Respiratory Health/Injury
Dr. Michel Sadelain, Sloan Kettering Institute for Cancer Research
Product: Chimeric Antigen Receptor Therapy for Mesothelioma, Other Cancers that Express Mesothelin
Award Mechanism: Technology/Therapeutic Development Award
Dr. Sadelain engineered T cells to recognize mesothelin, an antigen specific for malignant pleural mesothelioma, and developed a novel approach to deliver the engineered T cells by infusing them directly into the pleural cavity, a technique that was 30 times more effective than the traditional T cell therapy method of intravenous administration.

Portfolio: Internal Medicine
Dr. Jianguo Cheng, Cleveland Clinic Foundation and Dr. Tingyu Qu at the University of Illinois at Chicago
Product: Method for Stem Cell Transplantation for Pain Management
Award Mechanism: IIRA- Partnering PI Option
Drs. Cheng and Qu identified methods for using stem cell transplantation for long-lasting pain management with decreased morphine tolerance.

2012

Portfolio: Autoimmunity/ Immunology
Anie Philip, McGill University Health Centre Research Institute
Product: CD109 as a Novel TGF-beta Antagonist and Anti-Fibrotic Agent for the Treatment of Scleroderma
Award Mechanism: IIRA
Dr. Philip identified a CD109 peptide that is highly potent at inhibiting the production of collagen and extracellular matrix proteins which cause scarring in skin cells, and will be developing the peptide into a novel anti-fibrotic agent for treatment of systemic scleroderma.

Portfolio: Infectious Disease
Todd Giorgio and Timothy Cover, Vanderbilt University
Product: Fluidic Device for the Detection, Capture, or Removal of a Disease Material
Award Mechanism: IIRA- Partnering PI Option
PRMRP-supported research by Dr. Giorgio led to the foundation of PATH EX, a company that is developing an extracorporeal blood cleansing device designed to selectively remove pathogens, including multi-drug resistant bacteria and endotoxins, from circulating blood.

2014

Portfolio: Cardio
Nikolay Vasilyev, Children's Hospital, Boston
Product: Ventricular Assist Device
Award Mechanism: Discovery Award
Dr. Vasilyev designed a minimally invasive, implantable intra-cardiac device designed to support blood ejection from the ventricle for patients with heart failure awaiting transplantation. The device will prevent the need for cardiopulmonary bypass, significantly reducing the need for anticoagulation treatment and associated adverse events such as bleeding or thromboembolism.

2009

Portfolio: Neuro/Psych Health
Thanos Tzounopoulos, University of Pittsburgh
Product: Potassium Channel Openers to Prevent Tinnitus Development
Award Mechanism: IIRA
Dr. Tzounopoulos discovered that two types of ion channels found in neurons within the dorsal cochlear nucleus are crucial for resilience to noise-induced tinnitus. He is now developing novel drugs that modulate those channels for the prevention of tinnitus.

Portfolio: Autoimmunity/ Immunology
Jeffrey Cohen, Cleveland Clinic Foundation
Product: MSC Transplantation for Multiple Sclerosis Treatment
Award Mechanism: Clinical Trial Award
Dr. Cohen conducted a Phase I clinical trial which showed that autologous mesenchymal stem cell transplantation in patients with relapsing forms of MS is a safe and well tolerated therapeutic approach for the treatment of MS.

2013

Portfolio: Internal Medicine
Dr. Prakash Narayan at Angion Biomedica Corporation
Product: ANG3070, A Novel Kinase Inhibitor with Oral Bioavailability and Potential to Treat Chronic Kidney Disease
Award Mechanism: Technology/Therapeutic Development Award
Dr. Narayan demonstrated that a novel oral drug, ANG3070, decreases renal fibrosis and inflammation in preclinical models of chronic kidney disease that incorporate age and metabolic syndrome, two common comorbidities. The results support a planned filing with the FDA and transition of ANG3070 into clinical testing.

2011

Portfolio: Autoimmunity/ Immunology
Lisa Laury-Kleintop, Lankenau Institute for Medical Research
Product: Novel Therapeutic Target for the Treatment of Lupus
Award Mechanism: Discovery Award
Dr. Laury-Kleintop showed that targeting the small GTPase RhoB with a monoclonal antibody significantly decreases autoantibody levels in a preclinical model of systemic lupus erythematosus without affecting overall B-cell function, identifying anti-RhoB biologics as novel potential therapeutics for lupus.

Portfolio: Internal Medicine
Dr. Dennis Roop, University of Colorado, Denver and Dr. Jakub Tolar at University of Minnesota, Twin Cities
Product: Protocol for patient-derived stem cell based gene editing therapy for epidermolysis bullosa
Award Mechanism: IIRA- Partnering PI Option
Drs. Roop and Tolar developed protocols for a patient-derived, SC-based gene editing therapy for epidermolysis bullosa, a skin disorder that causes severe blistering and scarring. Dr. Roop's group received additional funding in FY17 to translate this technique into the clinic.

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 loss of fitness for military 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

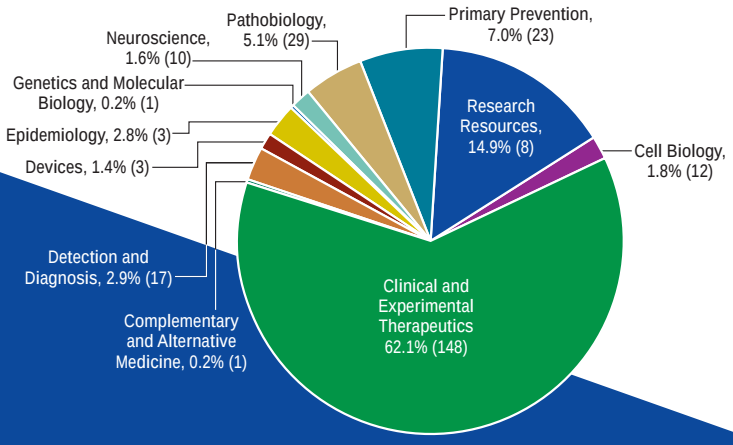
Over half of all combat injuries sustained during OIF and OEF involve extremity injuries and orthopaedic-specific conditions secondary to battle injury represent the largest source of long-term disability in returning Service members.[1] The impact of these injuries points to an urgent need for orthopaedic research that provide superior medical care and treatment options for injured Service members. PRORP crafts investment strategies to address and consider all aspects of orthopaedic injury, as well as other related medical challenges, with the goal of helping injured Service members and Veterans achieve optimal recovery from combat and combat-related orthopaedic injuries. Since its inception in FY09, the PRORP has dedicated its congressional appropriations, totaling $368.5M, toward supporting military-relevant orthopaedic research with the expectation that any research findings will also benefit the general population.

The PRORP has funded more than 250 awards through FY17 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 orthopaedic care.

[1] Cross JD, Ficke JR, Hsu JR, et al. 2011. Battlefield orthopaedic injuries cause the majority of long-term disabilities. *J Am Acad Orthop Surg* 19:S1-S7.

"I am humbled to serve as a consumer reviewer on the prosthetic and orthotic panels and give firsthand commentary regarding how future devices will impact the lives of Soldiers and civilians alike. With each meeting that I attend, my admiration grows for the dedicated and professional scientists that are committed to trying to understand what it's like to be the end user of the science. They are receptive to what the consumers say regarding their experiences and value those shared expressions."

SFC (ret.) Rickey Williams
PRORP Consumer Peer Reviewer



FY09-FY17 PRORP Portfolio Investment by SCS Code

IMPROVING FUNCTIONAL OUTCOMES OF COMBAT-INJURED WARFIGHTERS BY RELIEVING POST-AMPUTATION PAIN

Joseph Boggs, PhD, SPR Therapeutics, Inc. (a portfolio company of NDI Medical, LLC)

A significant number of Service members living with combat-related traumatic amputations suffer from moderate to severe post-amputation pain. Unfortunately, many do not find relief from current therapies on the market, resulting in a significant number of these individuals not being able to 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. In FY12 the PRORP awarded Dr. Joseph Boggs with a Clinical Trial Award to study percutaneous peripheral nerve stimulation using the SPRINT® PNS System (SPR Therapeutics, Inc., Cleveland, Ohio; https://www.sprtherapeutics.com) designed to reduce the risk of complications and enable delivery of stimulation without surgery. In a previous study, the percutaneous PNS system provided pain relief and improved functional outcomes in at least 75% of amputees. The therapy involves the insertion of a fine-wire coiled lead through an introducer needle to target one or more peripheral nerves. A review conducted to compare the use of a coiled versus non-coiled design found that percutaneous leads used for neurostimulation of the peripheral nervous system have a much lower risk of infection with a coiled design compared with non-coiled leads. The goal of the Clinical Trial Award was to collect data on the safety and effectiveness of the percutaneous PNS therapy in improving functional outcomes by alleviating pain in individuals with major lower limb amputations. The project has successfully achieved its goal of demonstrating clinically and statistically significant reductions in post-amputation pain and pain interference from use of the percutaneous PNS system.

DEVELOPMENT OF A HIGH-PERFORMANCE, ADAPTABLE PROSTHETIC SOCKET FOR AMPUTEES

Jason Wheeler, PhD, Sandia National Laboratories

There are nearly 2 million Americans living with the loss of a limb. Unfortunately, despite improvements to overall function of modern prosthetics, the fit and comfort of the prosthetic limb are often the deciding factors in prosthetic use or abandonment. With support from an FY09 PRORP Technology Development Award, Dr. Jason Wheeler and his team have addressed specific issues in the maintenance or enhancement of long-term socket performance and the fit of prosthetic devices for both above and below the knee amputees. The three goals of Dr. Wheeler's work were to develop a socket liner that could monitor the volume and shape changes of the residual limb, adapt to these changes in real time, and provide sensory feedback to the wearer regarding joint position and prosthetic movement. In order to track changes in the residual limb, Dr. Wheeler and his team developed a novel sensor embedded within a silicone liner that could measure normal and shear pressures. This new technology represents an exciting new capability not available in other sensor systems. Taking this work a step further, Dr. Wheeler also incorporated a system of bladders, or channels, into the liner that can alter their fluid volume in response to changes in residual limb size or shape, as detected by the pressure sensors. Preliminary tests with patients found that the liner adjusted well to changes in limb volume during laboratory use and was comfortable to wear.

Refinement and development of Dr. Wheeler's sensory and adaptive socket liner as it moves toward clinical availability is ongoing, with increased patient testing (in collaboration with Dr. Joan Sanders at the University of Washington) and improved manufacturing of the device to transition the sensor system to market for use with multiple prosthetics.

"The PRORP encourages multidisciplinary collaboration between military, other governmental, and civilian personnel to leverage their individual expertise and augment the number of patients enrolled in clinical trials so that requisite sample sizes are met. The benefits of maintaining this military civilian-partnership is the ability to investigate and draw meaningful conclusions to the major gaps in orthopaedic and rehabilitation research defined by the military."

COL (ret.) Philip Belmont
PRORP Co-Chair, FDA Division of Orthopaedic Devices

Prostate Cancer Research Program

VISION
Conquer prostate cancer.

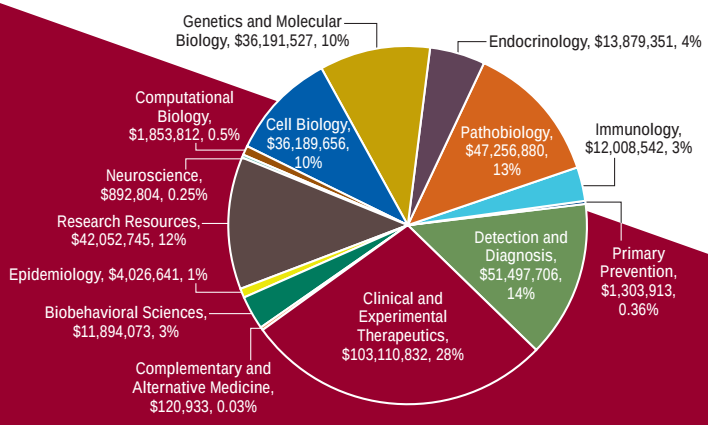
MISSION
Fund research that will lead to the elimination of death from prostate cancer and enhance the well-being of Service members, Veterans, and all men experiencing the impact of the disease.

PROGRAM HISTORY
Since its inception in 1997 and over its 21-year history of congressional support totaling nearly $1.72B, the PCRP has changed the landscape of biomedical research and energized the prostate cancer (PCa) research community to conduct high-risk research that is decidedly collaborative, innovative, and impactful, ultimately aiming to conquer the disease. The PCRP has made unprecedented inroads in supporting the development of new treatments for advanced PCa; has been the leading supporter of research aimed at understanding and resolving ethnic disparities in PCa incidence and mortality; and has fostered the development of over a thousand young investigators, many of whom have become leaders in cutting-edge research that is making a significant difference for millions of patients with PCa.

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.

- 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
- Improve the quality of life for survivors of prostate cancer

PROGRAM PORTFOLIO
The PCRP strives to diversify its research portfolio with different scientific approaches, ultimately focused on addressing the critical needs of PCa patients. Supported projects range from innovative, exploratory studies to larger projects focused on transforming PCa clinical care, all of which are working towards making a direct, positive impact on patients and their families.



FY13–FY17 PCRP Portfolio Investment by SCS Code

CLINICAL BREAKTHROUGH

Apalutamide received FDA-approval in 2018 as the first anti-androgen therapy approved for treatment of non-metastatic castration resistant prostate cancer (CRPC). The PCRP-funded PCCTC was instrumental in the early phase trials that led to its approval.

Steven Patierno, PhD, Duke University

With the support of an FY13 Health Disparity Research Award, Dr. Steven Patierno and his collaborators at the George Washington University are investigating how alternative RNA splicing (ARS) may contribute to prostate cancer health disparity in African Americans. Comparing ARS variants in prostate cancer from African Americans and Caucasian Americans revealed more than 2,500 differences, including identification of a gene not previously associated with prostate cancer as an ARS variant present in African American prostate cancer patients. The team found that this ARS variant, phosphoinositide 3-kinase delta (PI3KΔ)-short, is linked to aggressive prostate cancer and is resistant to current PI3KΔ inhibitors. This work underscores the need to identify new molecular targets for prostate cancer prognosis and therapies, especially in vulnerable populations. Dr. Patierno's ongoing research may help close the health disparity gap for African American prostate cancer patients and lead to more effective cancer prognosis and therapies for all men.

Scott Dehm, PhD, University of Minnesota, Twin Cities, and Manish Kohli, MD, Mayo Clinic

Through an FY14 Synergistic Idea Development Award, Drs. Scott Dehm and Manish Kohli are utilizing a prospective clinical trial at the Mayo Clinic, called PROMOTE (Prostate Cancer Medically Optimized Genome-Enhanced Therapy), as a platform for identifying genomic alterations associated with primary and acquired resistance to the androgen-deprivation therapy (ADT) abiraterone. Next-generation sequencing of metastatic biopsies determined that genes in the Wnt/β-catenin pathway mutated more frequently in patients who did not initially respond to abiraterone treatment. They also leveraged the PROMOTE trial to discover AR-V9 as an AR variant frequently co-expressed with AR-V7 in prostate cancer. Importantly, high AR-V9 expression in metastatic tumor biopsies was predictive of resistance to abiraterone. Drs. Dehm and Kohli are currently analyzing post-abiraterone tissue samples to further characterize genetic mutations in tumors with acquired resistance, and evaluating therapeutic vulnerabilities in mouse models. This research could guide future studies in identifying biomarkers for predicting resistance, as well as lead to novel drug targets and therapeutic approaches for patients with CRPC.

Colin Pritchard, MD, PhD, University of Washington

Dr. Colin Pritchard developed a highly innovative and robust method for detecting microsatellite instability (MSI) in tumors, called the MSI by next-generation sequencing (mSINGS) method. Present in roughly 15% of patients with advanced PCa, MSI is associated with a subtype of PCa with a high number of DNA mutations (i.e., hypermutations) and could predict responses to therapy. Using an FY13 Physician Research Training Award, Dr. Pritchard showed that MSI is the major mechanism leading to hypermutation in PCa and found the mSINGS method to be superior to traditional assays that detect MSI. This research has led to support of a clinical trial that will use an mSINGS-based assay to identify participants with hypermutated MSI PCa for checkpoint blockade immunotherapy. Additionally, MSIplus, an assay based on mSINGS, is now validated for both PCa and colorectal cancer. Ultimately, the mSINGS method could serve as a low-cost, rapid, highly sensitive tool for MSI detection that could replace traditional assays and predict therapy responses for patients with this unique subset of PCa.

"The PCRP promotes results-oriented, cutting-edge research into prostate cancer's origin, diagnosis, treatment, and post-treatment care. Military service members and Veterans, including myself, are a reflection of our population at large, and must effectively deal with the health conditions of its personnel to maintain a viable fighting force. The PCRP is one of those tools that help maintain a healthy fighting force."

Don Triplett
Us TOO International, Inc.

Reconstructive Transplant Research Program

VISION

Unlocking the full potential of reconstructive transplantation.

MISSION

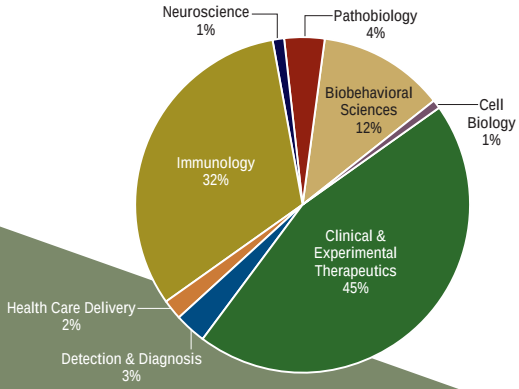
Developing innovative solutions for the field of vascularized composite allotransplantation to expand public awareness, enhance patient selection, and optimize the restoration of form, function, appearance, and psychosocial health for catastrophically injured military Service members, Veterans, and American civilians.

PROGRAM HISTORY

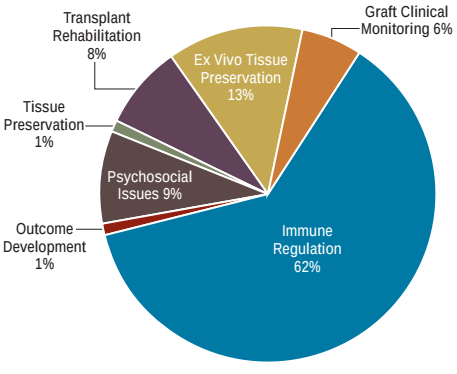
The Reconstructive Transplant Research Program (RTRP) was established in FY12 to provide support for research of exceptional scientific merit that has the potential to make a significant impact on improving the function, wellness, and overall quality of life for injured military Service members and Veterans, 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 $81M in appropriations though FY18.

RTRP FY18 FOCUS AREAS

- Reduce the risks of VCA-associated immunotherapy
- Revolutionize *ex vivo* VCA tissue preservation strategies to extend the timeline between procurement and transplantation
- Identify near- and long-term functional, quality of life, and psychosocial outcomes in VCA and their influencing factors



RTRP Portfolio Investment by SCS Code



RTRP Portfolio Investment by Focus Area

"The CDMRP RTRP provides an excellent opportunity to progress a rapidly developing, cutting-edge field. I'm very impressed by the scientific diversity within the review panel, as well as in the proposals we review. The science and technology being developed from this program are unique and provide an interesting perspective on how to approach the challenges associated with advancing VCA solutions."

Matthew Wood
RTRP Programmatic Panel Member

CONSUMER INVOLVEMENT

COL (Dr.) Robert T. Frame was leading a Civil Affairs Command Public Health Team in Baghdad when he was critically injured in an ambush in April 2003, leaving his left hand and arm almost non-functional due to tissue loss and vascular atrophy. Returning to duty as the Assistant Under Secretary of Health for Dentistry in the VA, Dr. Frame eventually transitioned to the role of National Returning Warriors Liaison for the Vet Centers Readjustment Counseling Service, where he worked to assist and counsel other Veterans and their families. Dr. Frame has served as a consumer peer reviewer for the RTRP since 2011 and joined the RTRP Programmatic Panel in 2016. Dr. Frame says, "As consumer reviewers, we are the voice for many wounded warriors and their families and caregivers. We bring many different experiences and skills to the table. Through this diversity we help complete the circle. We are not defined by our injuries or the harshness we experienced, but by what we have learned and how we have grown through the adversity. We appreciate this opportunity and we take it very seriously."

RESEARCH HIGHLIGHTS

T-REGULATORY CELL-BASED THERAPIES PROMOTE SURVIVAL OF VASCULARIZED COMPOSITE ALLOGRAFTS

Wayne W. Hancock, MD, PhD, Children's Hospital of Philadelphia

A potential solution for catastrophic tissue loss is VCA, which replaces large sections of composite tissue (e.g., a hand or face). Despite great promise, VCA has been limited by the requirement for lifelong immunosuppression therapy to prevent allograft rejection. T-regulatory cells (Tregs) could represent an alternative treatment, as they suppress the effects of other T cells that participate in transplant rejection. In particular, Dr. Hancock found that Tregs expressing the transcription factor Foxp3 (Foxp3+ Tregs) are key to immune tolerance and depend on the interleukin-2 (IL-2) signaling molecule for survival. Administering an IL-2/anti-IL-2 monoclonal antibody complex (IL-2C) to naïve mice was found to increase Foxp3+ Tregs by 10-fold. When tested in a mouse model of VCA before or after forelimb transplantation, IL-2C therapy prolonged allograft survival 3-fold (21 days, compared to 7 days in saline-treated control animals; $p<0.001$). The combination of pre-transplant IL-2C therapy with post-transplant rapamycin administration led to greater than 50 days of VCA survival with no signs of rejection ($p<0.001$ compare to saline-treated controls). This work illustrates the potential for Foxp3+ Treg-based therapies to serve as an alternative approach for immune system modulation and as an anti-rejection strategy.

BIOMARKERS TO PREDICT REJECTION IN VASCULARIZED COMPOSITE ALLOTRANSPLANTATION

Leonardo Riella, MD, PhD, Bohdan Pomahac, MD, Thet Su Win, MD, PhD, Brigham and Women's Hospital, Inc.

VCA can transform lives after devastating injury or significant tissue loss. These improvements in quality of life, however, carry risks associated with lifelong immunosuppression. Dr. Riella and his team hypothesize that biomarkers of early allograft rejection can assist in timelier intervention and reduce exposure to anti-rejection medications. In addition, molecular biomarkers may be able to distinguish the mechanism of rejection, such as antibody-mediated rejection (AMR) and T cell-mediated rejection (TCMR), which require different treatment strategies and diagnostic criteria. A comparison of gene expression in facial allograft biopsies revealed 79 upregulated genes and 1 downregulated gene during rejection episodes. These findings demonstrated an activation of the interferon-gamma pathway, and also of genes associated with cytotoxic cell recruitment and immune effector function. This gene expression pattern is consistent with the presence of inflammation during allograft rejection. Further analysis identified 31 genes that contributed most to the variability between AMR and TCMR. AMR may be associated with a pro-inflammatory environment involving activation of the endothelium and recruitment of white blood cells to the allograft, whereas an increase in cell death-related signaling may be present during episodes of TCMR. This research could lead to improved clinical monitoring of VCA as well as new therapeutic targets for treating rejection.

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

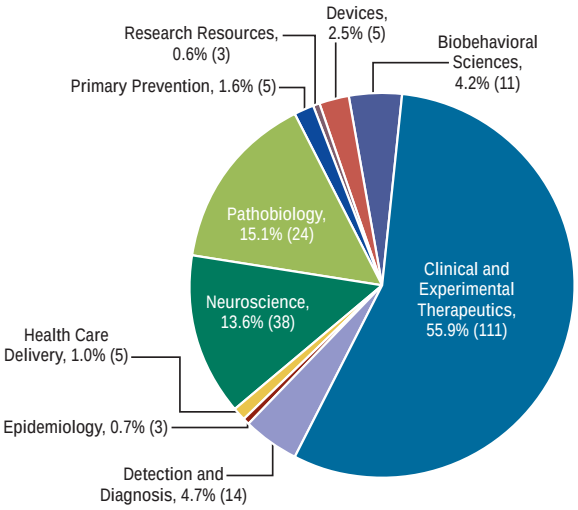
To fund research and encourage multidisciplinary collaborations for the development and translation of more effective strategies to improve the health and well-being of Service members, Veterans, and other individuals with spinal cord injury.

PROGRAM HISTORY

The Spinal Cord Injury Research Program (SCIRP) was established by Congress in FY09 to support research into regenerating/repairing damaged spinal cords and improving rehabilitation therapies. With $217.85M in congressional appropriations between FY09 and FY17, 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 219 awards through FY17 across basic research, pathology detection, and diagnosis of spinal cord injury (SCI), with the largest investment in clinical and experimental therapeutics—reflecting the program's emphasis on translational and clinical research.



FY09-FY17 SCIRP Portfolio Investment by SCS Code

"The process by which applications are reviewed is exemplary, particularly with respect to engagement of and collaboration among veterans, scientists, and clinicians. The program reflects an unwavering commitment to society by improving the lives of Veterans and civilians who live with the sequela of one of the most devastating injuries imagined."

MaryJane Mulcahey
FY17 SCIRP Peer Reviewer

"Having a mixture of scientific and consumer representatives participate in the peer review process maximizes impact and keeps research on target to the needs of the community for the projects supported by the SCIRP."

Robert Wudlick
FY17 SCIRP Consumer Reviewer

CLINICAL TRIALS IN SPINAL CORD INJURY

Over the last two years, SCIRP has funded four clinical trials for rehabilitation interventions to build on the plasticity in the remaining spinal cord to improve function and two clinical trials specifically targeting pain and depression - all with the goal of improving function and quality of life.

EFFECT OF A NOVEL INTERVENTION USING DAILY INTERMITTENT HYPOXIA AND HIGH-INTENSITY TRAINING ON UPPER-LIMB FUNCTION IN INDIVIDUALS WITH SPINAL CORD INJURY

William Rymer, Rehabilitation Institute of Chicago

THE USE OF ACUPUNCTURE IN POTENTIATING FUNCTIONAL RECOVERY IN SPINAL CORD INJURY SUBJECTS

Deborah Stein, University of Maryland Baltimore

TELEPSYCHOLOGY INTERVENTION FOR INDIVIDUALS WITH SPINAL CORD INJURY AND DEPRESSION

Kazuko Shem, Santa Clara Valley Medical Center

ACUTE INTERMITTENT HYPOXIA AND RESPIRATORY STRENGTH TRAINING TO IMPROVE BREATHING FUNCTION AFTER SCI

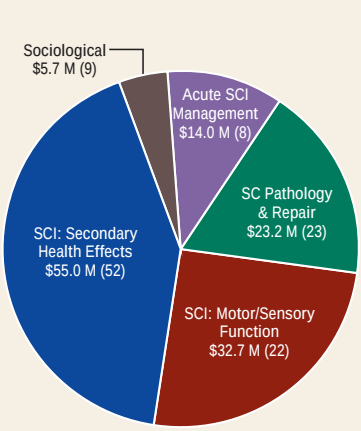
Emily Fox, University of Florida

MECHANISMS AND EFFICACY OF HIGH-INTENSITY VARIABLE TRAINING IN PATIENTS WITH INCOMPLETE SCI

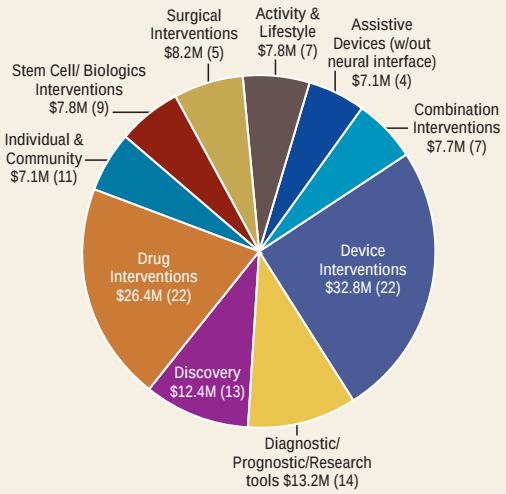
Thomas Hornby, Indiana University

IMPROVING SPINAL CORD INJURY REHABILITATION INTERVENTIONS BY RETRAINING THE BRAIN

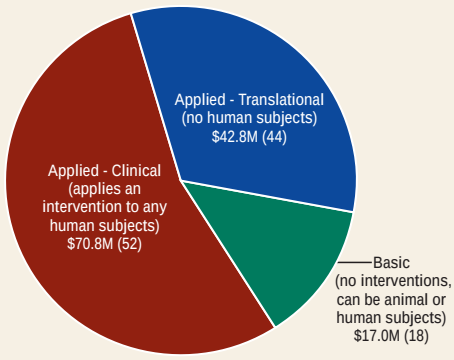
Ela Plow, Cleveland Clinic Foundation



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 of 114 active awards (funding shown by $ million 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 loss of muscle and bone, development of pressure ulcers, neuropathic pain, and respiratory and autonomic 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. As a program, although SCIRP does support basic research, the focus is on translational 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 and to deliver innovative solutions to prevent, diagnose, and treat their manifestations for the benefit of US Service members and the American public.

PROGRAM HISTORY

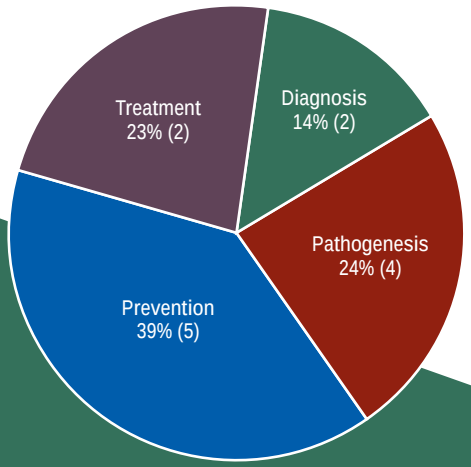
The Tick-Borne Disease Research Program (TBDRP) was established in FY16, when the efforts of Lyme disease advocates led to a Congressional appropriation of $5M. The TBDRP has received funding at a rate of $5M annually, totaling $15M for the period FY16-FY18. The intent of the TBDRP is to support innovative and impactful research that addresses fundamental issues and gaps in tick-borne diseases.

There are currently at least 16 known tick-borne illnesses, with emerging diseases being discovered all the time. In the United States, cases of Lyme disease and other tick-borne diseases, including spotted fever rickettsiosis, anaplasmosis, and ehrlichiosis, have been increasing steadily for years and currently total tens of thousands of people diagnosed annually, with more likely going undiagnosed.

Continued research efforts are needed to better understand tick-borne disease pathogenesis, including host-pathogen interactions and the human immune response to these pathogens. There is a need for better disease prevention in terms of controlling the natural cycle of disease and protecting people from tick bites by various means. For people who are bitten, having methods of direct detection of tick-borne pathogens is critical in guiding treatment, and more must be learned about the cause of persistent symptoms in Lyme disease and other tick-borne illnesses in order to establish the best treatments.

"I am thankful for the opportunity to be a consumer reviewer for the TBDRP. There are more questions than answers in this area of study, and any research that can be funded will bring us closer to understanding the complexities of tick-borne illness. Watching my daughter go from a healthy college athlete to a very sick young woman in a wheelchair, all while medical professionals were confused and at a loss, fueled my passion for change. I am honored to work with the staff and serve along side the best researchers in this field."

Tammy Crawford
Executive Director Focus on Lyme



FY16–FY17 TBDRP Portfolio by Focus Area

PROGRAM GOALS AND STRATEGY

The TBDRP offered three award mechanisms in FY18; the Career Development Award, the Idea Award, and the IIRA. These awards are focused in the following areas in Lyme disease and other tick-borne diseases, with emphasis on reducing the public health burden:

DIAGNOSIS:

- Accurate diagnostics for Lyme disease and co-infections and/or other tick-borne diseases
- Biomarkers to identify tick-borne diseases or their products in humans
- Diagnostic biomarkers for Lyme disease that distinguish between active infection and previous exposure, and/or monitor response to treatment

PATHOGENESIS:

- Understanding the immunological mechanisms of immune protection for Lyme disease or other tick-borne diseases
- Understanding the complex biology of Lyme borrelia in the host (beyond in vitro studies), including its survival, evasion of the host immune system, and subversion of the effectiveness of antibiotics
- Biomarkers that aid in exploring underlying mechanisms of persistent symptoms associated with Lyme disease

TREATMENT:

- Antibiotic combinations and/or therapeutic options for treating acute and persistent illness

PREVENTION:

- Identification, validation, and/or improvement of tick-targeted prevention and control interventions
- Human vaccines for tick-borne diseases

CONSUMER HIGHLIGHTS

NICOLE MALACHOWSKI: UNFIT FOR DUTY FROM DEBILITATING TICK-BORNE DISEASE

Nicole Malachowski medically retired from the US Air Force as a Colonel after 21 years of Service as a career fighter pilot. At only 43 years old, she was deemed unfit for duty due to neurological damage from tick-borne illness. In 2012, she began experiencing intractable pain, insurmountable fatigue, cognitive dysfunction, and speech impairment. These symptoms significantly impaired her ability to serve her country as well as her ability to provide for her children. Initially dismissed as originating from overstress, the symptoms persisted. In the end, it took over 4 years, more than 24 doctors, and multiple misdiagnoses before she was accurately diagnosed. Despite moderate improvement after her diagnosis, the battle is not over for Ms. Malachowski, who needs continued medical treatment. She remains concerned about the inadequacies in diagnostic testing and the treatment options available for patients with tick-borne illness, especially among military and Veteran communities, due to the high risk of exposure for active duty populations and military families. Ms. Malachowski has advocated for better tick-borne disease research, serving as a consumer peer reviewer for the TBDRP in FY17.

FORGOTTEN, BUT NOT GONE: ROCKY MOUNTAIN SPOTTED FEVER

On May 11, 2012, Gabby, a vibrant 5-year-old, succumbed to sepsis. Despite multiple visits to her pediatrician and two different emergency rooms, Gabby was continually misdiagnosed. From when her symptoms appeared on May 1, 2012, to when she was finally diagnosed as septic, Gabby had been misdiagnosed four times. Worse, Gabby had been sent home after a blood panel revealed clear indicators of sepsis. Her autopsy confirmed Rocky Mountain Spotted Fever (RMSF), the diagnosis that at least three of her attending physicians had considered but failed to treat, despite Gabby's fever and the iconic spotted rash spread across her body. Together Gabby's parents, Tony and Liz Galbo, have championed "Gabby's Law," which requires Illinois hospitals to be better prepared to recognize and treat sepsis. They have also campaigned to improve public health awareness by advocating for both required coursework for clinicians on local ticks and the diseases they carry and for public outreach programs that are coordinated through local and state public health departments. Tony Galbo joined the TBDRP in FY17, where he continues to advocate for improved resources for frequently overlooked illnesses such as RMSF.

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

"My experience with the TSCRP has been rewarding, enlightening, and empowering. The TSC community is fortunate that there is a dedicated commitment from the scientific community to understanding the pathogenesis and manifestations of TSC."

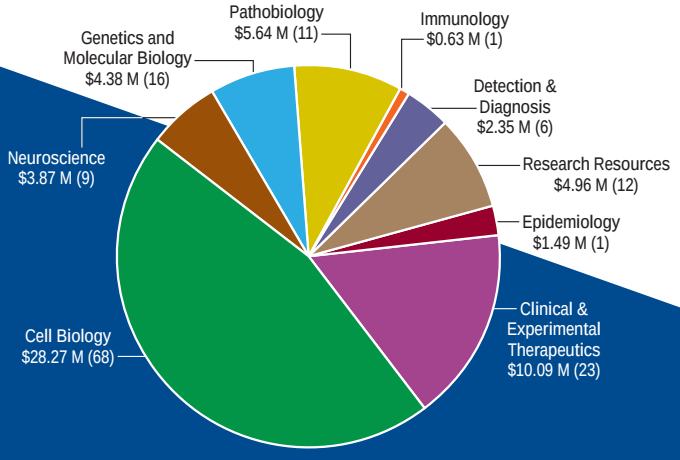
Shelly Meitzler
Consumer Peer Reviewer

PROGRAM HISTORY

Tuberous sclerosis complex (TSC) is a genetic disorder that causes non-malignant tumors in many different 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. The TSC1 and TSC2 genes are located on chromosome 9 and chromosome 16 respectively. 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 TSCRP was first funded in FY02 when the efforts of TSC advocates led to a Congressional appropriation of $1M. Since then, a total of $77M has been appropriated to the program, including $6M in FY18. Today, the TSCRP is one of the leading sources of extramural TSC research funding in the United States.

PROGRAM PORTFOLIO

The Tuberous Sclerosis Complex Research Program (TSCRP) has funded 147 awards through FY17 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.



FY02-FY17 TSCRP Portfolio Investment by SCS Code

"The TSCRP plays a critical and unique role in the funding landscape for TSC research. The TSCRP Programmatic Panel is responsible for setting the program's research funding priorities, and I feel privileged to contribute as a representative of the Tuberous Sclerosis Alliance (TS Alliance). By participating in the panel, I help ensure the TSCRP funding strategy is complementary with, and not duplicative of, the TS Alliance's research strategy, and vice versa. Along with TSC consumers on the Programmatic Panel, I also help ensure the focus and priorities of the TSCRP are driven by the needs of individuals affected by TSC, many of whom are children or siblings of military Service men and women and veterans. Because tuberous sclerosis complex causes tumors, autism, and epilepsy, among other things, what researchers learn from their TSCRP-funded work will help us understand and find treatments for related disorders including cancer, autism spectrum disorder, traumatic brain injury and epilepsy. The potential impact of the TSCRP is almost limitless, and I'm fortunate to help contribute to this important program."

Steven Roberds, PhD
TS Alliance, Programmatic Panel member

PROMISING THERAPEUTIC APPROACHES TO LESSEN THE IMPACT OF TSC

TOPICAL RAPAMYCIN THERAPY TO ALLEVIATE CUTANEOUS MANIFESTATIONS OF TUBEROUS SCLEROSIS COMPLEX

Mary Kay Koenig, MD, University of Texas Health Science Center, Houston

One of the many manifestations of TSC is the development of angiofibromas (red bumps on the face, especially on the nose and cheeks) that can slowly enlarge and cause significant textural changes to the skin. Although not life-threatening, they cause notable disfigurement and are one of the most significant features of TSC that impact a patient's life. Currently, there is no effective method for preventing or permanently removing the angiofibromas. mTOR inhibitors, such as rapamycin, are used as a first line of treatment for TSC. However, taken by mouth, rapamycin has side effects that limit its use to treat the skin symptoms of TSC. Knowing how beneficial mTOR inhibitors have been in TSC therapeutics, Dr. Koenig aimed to find a topical rapamycin therapy that could be used in those who were not candidates for oral therapy or could be used in combination with oral therapy to improve efficacy. With a TSCRP Clinical Research Award, Dr. Koenig established a multicenter clinical trial that allowed her and her team to successfully formulate and optimize the drug and controls. The formula was well-tolerated by patients and shown to be efficacious, with a dose response improvement. Since angiofibromas in individuals affected with TSC represent a major quality-of-life concern, the impact of this study is invaluable. Dr. Koenig plans to perform a follow-up study to confirm these exciting results, with an ultimate goal of petitioning the FDA for a formal indication for the treatment of facial angiofibromas.

A PROMISING EARLY INTERVENTION FOR TSC-LINKED AUTISM IN INFANTS

Shafali Jeste, MD, University of California, Los Angeles

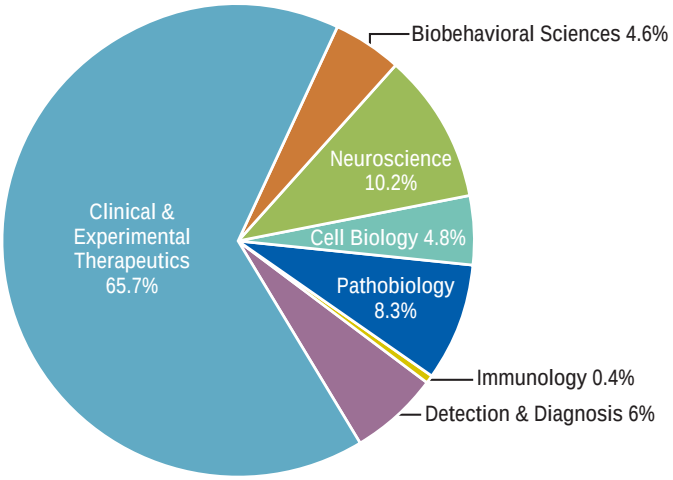
ASD occurs in approximately one-half of children with TSC, but is often diagnosed later due to the frequency of other medical and neurodevelopmental challenges early in infancy, making early interventions a huge challenge. However, because infants are diagnosed with TSC before the onset of autism, there is tremendous opportunity in studying signs of autism early in infancy in order to guide early interventions. Dr. Shafali Jeste used funding from a TSCRP Pilot Clinical Trial Award to follow up on early development and autism predictors in TSC identified in a previous TSCRP-funded study and investigate early intervention for autism in TSC. Based on the previous findings that demonstrated that infants with TSC who develop autism show delays in social and communication skills as early as 6 months of age, Dr. Jeste designed the pilot clinical trial to improve social skills in infants with TSC before they develop autism. The study investigators used a well-validated behavioral intervention, called JASPER (Joint Attention; Symbolic Play, Engagement, and Regulation), developed by Dr. Connie Kasari, a collaborator and expert in behavioral intervention for autism. The team examined the effects of this intervention on various behavioral outcomes as well as brain function in infants with TSC to determine if brain changes might predict changes in behavior. They found that infants showed improvements in their developmental skills after JASPER and made substantial gains in their development at a rate not seen in infants not receiving this targeted early intervention. This pilot clinical trial was the first study of early intervention in TSC, and its successes have since led to a large, NIH-funded, randomized control trial of JASPER in infants with TSC.

Vision Research Program

VISION
Transform vision trauma care for our armed forces and the nation.

MISSION
Improve the health and readiness of military personnel affected by eye injuries and vision dysfunction by identifying clinical needs and addressing them through directed medical research.

PROGRAM HISTORY
Eye injury and visual dysfunction resulting from battlefield trauma affect hundreds of thousands of Service members and Veterans. The Vision Research Program (VRP) was initiated in 2009 to fund impactful military-relevant vision research that has the potential to significantly improve the health care and well-being of military Service members, Veterans, their caregivers, family members, and the American public. Appropriations for the VRP from FY09 through FY17 totaled $70.2M. The FY18 appropriation is $15M. Since inception, 85 VRP applications have received funding to advance the understanding, prevention, diagnosis, mitigation, treatment and rehabilitation of eye injury or visual dysfunction.



FY09-FY17 VRP Portfolio Investment by SCS Code

"The Vision Research Program is vital for our wounded warriors to meet the goal of "Save Life, Eyesight, and Limb" on the battlefield. Both penetrating eye injuries and blast TBI vision dysfunction are critical trauma research areas that have been funded through VRP. Gaps in vision injuries are used to determine priorities for funding to improve outcomes in our Service members and Veterans with ultimate goal to restore vision from these catastrophic injuries."

Tom Zampieri
Blinded Veterans Association

APPLYING EXTRACELLULAR MATRIX TECHNOLOGY TO NEUROPROTECT AND REPAIR INJURED RETINAS AND OPTIC NERVES

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

Preserving vision after ocular damage is a long-standing challenge for researchers and clinicians. Once ocular damage has occurred, secondary inflammation and scar tissue forms in the injured CNS tissue, which impede vision, therapy, and repair. Dr. Badylak received a Translational Research Award in FY15 to generate an extracellular matrix (ECM) scaffold to aid in ocular healing by limiting inflammation and scarring. The ECM is to be utilized immediately after ocular damage, whether in the field or in general care. Dr. Badylak's accomplishments from this award have been in the form of seven publications and two patents. The publications highlight the ECM's mechanical and biochemical characteristics in addition to the results of in vitro testing for CNS repair. He has a patent on the ECM bio scaffolds, ECM hydrogels, and ECM bio hybrid sheets. This technology is in continuum for testing in animal models and, hopefully, eventual human clinical testing. If successful, ECM technologies will aid military Service members and the general public in preserving ocular reconstruction and will increase vision restoration.

NORLEU3-A (1-7) STIMULATES CORNEAL REPAIR AFTER INJURY

Dr. Gere diZerega, MD, U.S. Biotest, Inc.

Military service members are increasingly exposed to environmental conditions that cause ocular injury. These men and women lack adequate treatment when such injuries occur in the field. With his FY15 TRA, Dr. diZerega proposed to conduct preclinical testing of USB005, a preservative-free corneal repair drug delivered as a multi-use eye drop that could be used conveniently in the field. The formulation, dosage concentration, dosage frequency, and toxicity of USB005 were evaluated in rabbit models of corneal injury. Preclinical testing showed that repeated administration of USB005 was safe at all dosages and resulted in the repair of damaged tissues. In FY16, Dr. diZerega received a Clinical Trial Award to continue investigating USB005 in a Phase I clinical trial. Dr. diZerega and his team (led by Kainoa Peterson, Program Manager; Holly Maulhardt, Manufacturing Manager; Emily Williams, Regulatory Affairs Manager; as well as Leanne Drummond, Clinical Director and Alyson Marin, Clinical Support Associate), have already completed several aims of this Award, including GMP manufacturing of USB005, submission of an IND application for USB005 treatment of corneal injuries, FDA acceptance of the IND permitting the Phase I clinical trial to proceed. The final aim of the Clinical Trial Award is to conduct a Phase I, randomized, healthy volunteer, safety study, which is scheduled for completion in 2018. Follow-on Phase II study designs are being developed. Upon successful multi-phase clinical testing and submission of a New Drug Application (NDA), USB005 could become the first FDA-approved drug indicated for the treatment of corneal injuries.

RAPID DELIVERY OF PROTEIN THERAPEUTICS INTO RETINAL AND CORNEAL CELLS FOLLOWING INTRAVITREAL INJECTION

Dr. Rajendra Kumar-Singh, PhD, Tufts University School of Medicine

Intravitreal injection of therapeutics in ocular tissues has been shown to have positive clinical applications in repairing neurodegenerative and retinal disease. However, current clinical applications are only able to deliver proteins or large molecules extracellularly. In FY12, Dr. Kumar-Singh received an award under the BAA to characterize a nucleosomal binding protein and an aptamer (AS1411) as candidates that can pass through the retinal plasma membrane in vivo. These findings are now in parallel to Dr. Kumar-Singh's FY15 Technology/Therapeutic Development Award, through which he proposes to utilize AS1411 in combination with intravitreal injection to repair retinal degradation. Recently published results show successful intravitreal injection of X-linked inhibitor of apoptosis (XIAP) and other proteins into ganglion cells, photoreceptors, and retinal pigment epithelium in vivo. This approach enabled the attenuation of chemically induced apoptosis of retinal cells. This technology is the first proof-of-concept in delivery of large functional proteins and other macromolecules across the plasma membrane of retinal cells in vivo. In the long term, this platform technology has the potential to aid neurodegenerative and retinal diseases by aiding in the delivery of new pharmacologic agents.

Additional Supported DOD Programs/Projects

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

Clinical Research Intramural Initiative

MISSION

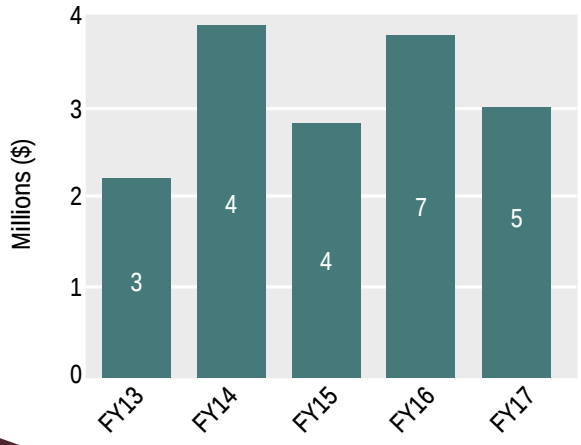
To promote and support biomedical research at MTFs for the benefit of the Service member, Veterans and beneficiaries.

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 MHS 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 23 awards through FY17 totaling approximately $15.7M to fund efforts in Intramural Initiated Research, Military Training Injuries, Health Services, Precision Medicine, and Military Women's Health.

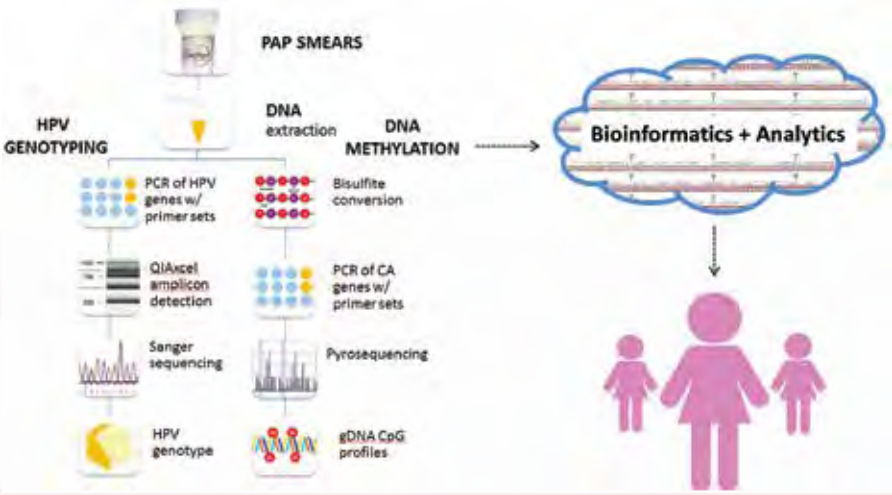


THE PAP SMEAR CHALLENGE: COMPARING CLINICAL PERFORMANCE OF A NOVEL "MOLECULAR PAP" BASED ON NEXT-GENERATION SEQUENCING TO TRADITIONAL CERVICAL CANCER SCREENING

J. Shen-Gunther, MD, PhD , COL, MC, Brooke Army Medical Center

Human Papillomavirus (HPV) is now recognized as the carcinogen of almost all invasive cervical cancers and a major cause of other human malignancies including oral and anal cancers, totaling approximately 600,000 cases annually worldwide. The Pap smear, regarded as the most successful cancer screening test in the history of medicine, has been in existence for over 70 years. However, due to the lack of Pap smear screening programs in developing countries or other social and economic barriers in developed countries, the rates of new cervical cancer cases and deaths remain high worldwide. To circumvent these challenges, COL Jane Shen-Gunther, developed of a molecular diagnostic test coined the Molecular Pap based on four molecular markers (Human Papillomavirus genotype and 3 epigenetic markers), innovative molecular technologies, and predictive analytics (or computerized classification). The Molecular Pap has tremendous practical value: (1) improved accuracy, (2) decreased laboratory costs, and (3) complementarity to home-based self-sampling.

With the support from the CRII award, COL Shen-Gunther continues to compare the diagnostic performance of the Molecular Pap to current cervical cancer screening methods in a head-to-head challenge using a large number of Pap smear samples from a military population. The ultimate goal is to translate their current discoveries into a cervical cancer screening test that is user-friendly, convenient, accessible, accurate, and affordable for women around the world. The next step is to further their work with academic and industry partners to develop a cloud-based automated bioinformatics pipeline. In parallel, a real-world data science workflow will be developed to curate computable laboratory data and implement machine learning with predictive analytics. The goal is to use artificial intelligence for speed and accuracy (in contrast to human subjectivity and errors) to create a better diagnostic test for cancer prevention. Looking forward, the methodologies and know-how developed by this project may be extended to other HPV-related cancers such as oropharyngeal and male anogenital cancers. Currently, screening tests for these cancers do not exist and are urgently needed.



The "Molecular Pap" is based on physician or self-sampled Pap smears, which undergo laboratory-based DNA extraction, HPV genotyping and quantitative DNA methylation of three genetic markers (left panel). Cloud-based bioinformatics and predictive analytics are then performed on the four molecular targets (HPV and three genetic markers) to classify cellular changes in the Pap smear and guide treatment of identified abnormalities. The ultimate goal is to develop an accurate, automated, low cost Pap smear with easy accessibility to results by women globally.

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 USAMRMC 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 USAMRMC, 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–FY17, CDMRP helped to manage approximately $710.1M 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 plans, coordinates, and oversees a responsive world-class, tri-Service science and technology program focused on three portfolios of research: (1) Medical Simulation (Med Sim), focused on improving military medical training through medical modeling, simulation, and educational training tools; (2) Health Information Technology (HIT), focused on improving the use and sharing of health-related data for better strategic planning, process development, and software applications; and (3) Multi-Domain Battle, an operational environment involving greater dispersion and near isolation over great distances, which is likely to cause severe restrictions on mobility for medical missions and shortfalls in both human and materiel human resources due to area denial challenges. MSISRP works with the Services and joint agencies to address gaps and requirements identified by the MHS and is responsible for programming research in the following areas:

- Medical Modeling, Simulation, and Training.
- Health Information Sciences

The establishment of MSISRP has enabled a more collaborative process to identify and validate research initiatives pertaining to the military. The program assists in identification, assessment, and transition of relevant emerging technologies that are of value to the MHS. This ultimately allows USAMRMC and the DHA J9, Research and Development Directorate, to better align research and development efforts with the needs of the MHS. Additional information about MSISRP is available at: http://mrmc.amedd.army.mil/index.cfm?pageid=medical_r_and_d.msis.overview.

Recent MSISRP DHP Research

- Translational Simulation Research – *Dr. Rosemarie Fernandez at University of Florida*
- Foundational Research for Autonomous, Unmanned, and Robotics Development of Medical Technologies – *Dr. Juan Wachs at Purdue University*
- Theater Operational Medicine Initiative – *Mr. James Beach at Telemedicine and Advanced Technologies Research Center*

Affiliated Research Programs

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

MILITARY INFECTIOUS DISEASES RESEARCH PROGRAM

MIDRP supports research and development 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

- Broad Spectrum Host-Oriented Therapy for Wound Infection – *Alan Cross at University of Maryland Baltimore and Raymond Kaempfer at Hebrew University of Jerusalem*
- Synthetic Engineering of Bacteriophage for Treatment of Wound Infections – *Derrick Fouts at J. Craig Venter Institute and Mikeljon Nikolich at WRAIR*
- Bioengineered commensals to fight S. aureus – *Julia Oh at Jackson Laboratory*

Affiliated Research Programs

- JWMRP
- TBDRP
- PRMRP

MILITARY OPERATIONAL MEDICINE RESEARCH PROGRAM

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*
- Brief Cognitive Behavioral Therapy (BCBT) Replication Trial – *Craig Bryan at University of Utah*
- 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 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:

- Hemorrhage Control and Resuscitation
- En Route Care
- Forward Surgical and Intensive Critical Care
- Neurotrauma and Traumatic Brain Injury
- Traumatic Tissue 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

- On-Demand Production of Human Platelets in an Automated Microfluidic Bioreactor – *Jonathan Thon at PLATELET BIOGENESIS, INC*
- Peptide-Based Dressings for Treatment and Control of Wound Infections – *Nina Bionda at iFyber, LLC*
- Gender Differences in Complement-Mediated Reperfusion Injury – *Sherry Fleming at Kansas State University*

Affiliated Research Programs

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

RADIATION HEALTH EFFECTS RESEARCH PROGRAM

RHERP seeks to develop medical countermeasures for acute ionizing radiation injury. Research areas include post-exposure mitigation of radiation injury, protection and prevention of injury from ionizing radiation, understanding the mechanism 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

- A Systems Biology Approach to Radiation Biodosimetry and the Host-Environment Interaction: Applications to Mass Casualty Triage in the Polytrauma Patient – *Robert Christy at USAISR*

Affiliated Research Programs

- JWMRP
- PRCRP
- PRMRP

CLINICAL AND REHABILITATIVE MEDICINE RESEARCH PROGRAM

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 FY17, CDMRP has managed 521 PH/TBIRP awards, totaling over $978.2M 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 MHS. Additional congressional appropriations for PH/TBIRP were assigned to USAMRMC between FY09 and FY17, and a modified execution model was established in which strategic oversight is provided by USAMRMC-based research program areas aligned with the OASD(HA). As directed by the OASD(HA), the DHA Research and Development Directorate manages and executes the DHP RDT&E appropriation, which includes the PH/TBIRP. The DHA Research and Development Directorate leverages PH/TBIRP funding to support ongoing research and development in DHP research program areas relevant to PH and TBI.

The JPCs/PADs provide recommendations to the DHA, 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, where 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 CSI funds to complement core DOD research and development 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

- Lesbian, Gay, and Bisexual Couples in the Military: A Post-DADT Examination of Relationship Health, Perceived Community Acceptance, and Mission Readiness – ***Jeffrey Cigrang at Wright State University***
- Peer Social Support During In Vivo Exposure for PTSD: A Program to Address Dropout from Prolonged Exposure – ***Ronald Acierno at Medical University of South Carolina***
- Reporting Practices of Medically-Diagnosed Child Maltreatment Among United States Army Families – ***David Rubin at Children's Hospital, Philadelphia***

CCCRP

- Evaluating Effectiveness of NFx101 for Reducing Brain and Peripheral Organ Injury and Improving Survival in a Combined TBI with Uncontrolled Hemorrhage Model – ***Brian Johnstone at NeuroFx, Inc***
- Development and Evaluation of a Solid State Head CT – ***Yueh Lee at University of North Carolina at Chapel Hill***
- Intelligent Mobile Ultrasound for Noninvasive Intracranial Pressure Estimation in Prehospital and PFC Settings – ***Balasundar Raju at Philips Electronics North America Corporation***

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***

OASD(HA)

The FY17 PH/TBIRP Applied Behavior Analysis (ABA) Clinical Study Award was awarded to Dr. Cynthia Johnson at the University of Rochester. Early Intensive Behavioral Therapy (EIBI), which can involve over 20 hours a week of intervention, is considered the standard of care for young children with ASD. This newly funded study will investigate whether an individualized approach, called adaptive, modular ABA (AM-ABA), could be as effective as EIBI for military beneficiates diagnosed with ASD. This approach adapts and combines targeted interventions aimed at improving specific core deficits related to social communication. If successful, AM-ABA could potentially reduce the time burden associated with standard of care EIBI on children with ASD and their families.

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 develop topics that address military medicine needs and provide management oversight of R&D projects, in support of broader SBIR/STTR goals.

PROGRAM HISTORY

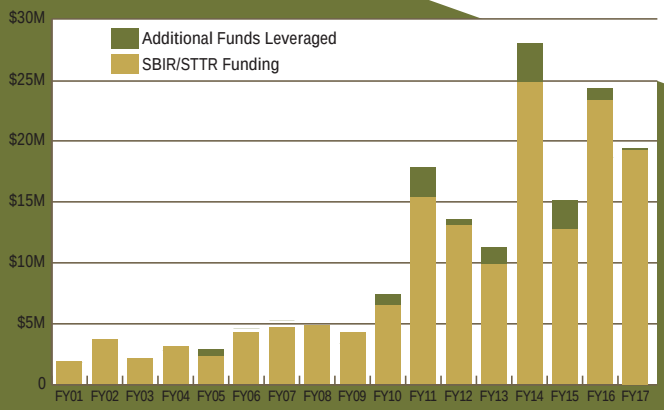
Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) are highly competitive programs that encourage US small businesses to engage in research and development with the incentive to profit from the product's commercialization. The programs are organized in three phases: 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 the SBIR and STTR programs since FY00 and FY04, respectively, to advance health and medical solutions for Warfighters and their families. CDMRP does this in coordination with JPCs and PADs by developing topics that address unmet military medicine needs. After a rigorous review process, approved CDMRP topics are announced on the DOD SBIR/STTR website, (http://www.acq.osd.mil/osbp/sbir/solicitations/index.shtml), under the Army or DHA components. CDMRP reviews proposals from small businesses, provides management oversight for the resulting awards, and coordinates with key stakeholders through all phases of development.

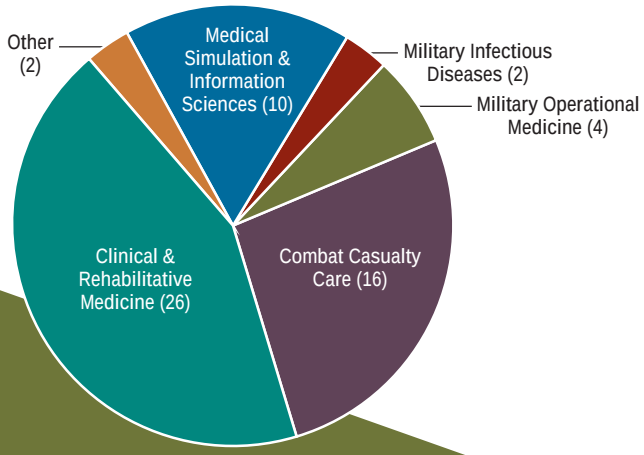
Projects Advancing Through the Phases

Topic Solicitation Year	Topics Managed by CDMRP	Phase I Awards	Phase II Awards	Additional Funding*
2011	14	50	18	4
2012	9	30	9	4
2013	10	17	15	1
2014	2	6	4	2
2015	9	22	13	0
2016	5	19	9	0
2017	8	25	13+	0
Totals	**56**	**170**	**68+**	**11**

+ Additional Phase II selections are pending.
*** Includes 2nd Phase II, Phase II Enhancement, and Phase III awards.**

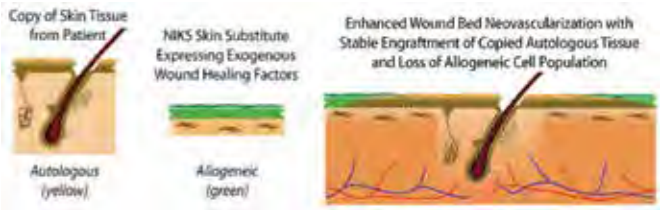


Total SBIR/STTR Funds Managed by CDMRP



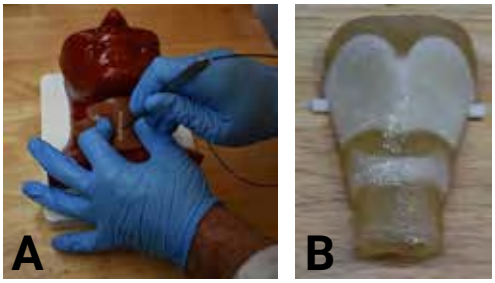
Topics by Program Area (since FY11)

SKIN SUBSTITUTE TECHNOLOGY FOR CHIMERIC AUTOLOGOUS/ALLOGENEIC CONSTRUCTS FOR SKIN REGENERATION



Clinicians currently manage severe traumatic skin injuries at risk of life-threatening complications by skin transplantation from an uninjured area. However, harvesting skin for transplantation creates a painful secondary wound at risk for infection, scarring, and other complications. Additionally, the transplanted skin is not fully functional and frequently lacks hair follicles, sweat glands, and other skin structures. Although harvesting and transplantation of small columns of full-thickness skin has the potential to regenerate fully-functional skin without the complications of current skin grafting procedures, adequate vascularization is needed to enable survival of the grafted tissue columns. Through Phase I and Phase II SBIR funding, Mallinckrodt's Stratatech Company is developing a living human skin substitute that expresses proteins that may promote blood vessel formation to enhance the survival of full-thickness skin columns. Ongoing efforts funded by the Phase II program are designed to complete process development, establish shelf life of the cryopreserved tissue, and perform preclinical safety studies necessary to support an Investigational New Drug application submission and initiation of ExpressGraft™ vascular skin substitute clinical evaluation.

3D PRINTING OF NEXT GENERATION SURGICAL TRAINING MODELS



A) Emergency cricothyoidotomy training model with simulated incision
B) Multi-material 3Dprinted trachea

Low-cost, high-fidelity anatomically accurate synthetic tissue models are needed for a number of applications such as surgical training, anatomy education, and pre-operation visualization. In order to overcome the barrier of expensive cadaveric training models while allowing students to practice medical procedures regularly in order to acquire and retain skills, Advanced Life Technologies LLC (ALT) has developed a novel, low-cost, additive manufacturing (AM) platform for synthetic tissue deposition. ALT LLC under DHA Phase I and Phase II contracts is developing 3D printing technology that allows the fabrication of heterogeneous synthetic tissues with lifelike skin, bone, fascia, adipose, muscle, and sensor materials. This technology will enable the next generation of surgical training models with improved fidelity and ability to record a user's manipulation of tissue during a simulated procedure. One application of this technology is illustrated as an emergency cricothyroidotomy training model which helps develop the skills to save lives in the field.

ADAPTING SMARTPHONES FOR OCULAR DIAGNOSIS

Smartphone Slitlamp/Ophthalmoscope Attachment for Ocular Diagnosis in the Field

The last century has brought an almost tenfold increase in the ocular injury rate on the battlefield, and the eye casualty rate in combat is 20 to 50 times greater than would be expected from the frontal area taken up by the ocular region. Add to this the fact that there are very few eye doctors deployed in field hospitals, and there is clearly a large need for a portable eye examination system that can help trained medical personnel diagnose eye injuries either on site, or remotely via telemedicine if they are not deployed to a given field hospital. SA Photonics has designed a portable slitlamp/ophthalmoscope on a CDMRP SBIR Phase I and II that has transitioned to US Army Medical Materiel Agency (USAMMA) via enhancement funding. Our system clips onto a smartphone and is easy to use for an untrained medic. The design is also capable enough so that an optometrist, ophthalmologist, or ophthalmic surgeon could use it in the field or in a hospital.

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
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. From FY16-FY18 Congress has invested $10M per year to the TCRP, and the FY16-FY17, appropriations were assigned to CDMRP for management and execution in partnership with the USAMRMC CCCRP. In FY18, strategic oversight of the TCRP transferred to the CCCRP and CDMRP provides award management support as needed.

LINKING INVESTIGATIONS IN TRAUMA AND EMERGENCY SERVICES
The FY16 and FY17 TCRP congressional appropriations have supported the Linking Investigations in Trauma and Emergency Services (LITES) contract. Released in June 2016 and awarded to the University of Pittsburgh, the LITES contract was executed to establish a multi-institution clinical research network to address military-relevant priorities and gaps in trauma care. With limited ability to conduct multicenter, large scale, high-impact, clinical research on deployed military personnel in active theaters of war, the DOD and its CCCRP decided to turn to civilian trauma systems and medical centers to answer trauma and treatment questions aimed at narrowing high-priority gaps in the care of severely injured patients. The LITES contract is not a singular research effort. Through the task order generation process, independent research studies and/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 2018, there are 17 LITES Network Sites and additional information is located at www.litesnetwork.org.

"The ultimate results of Task Order #01 may change the way we look at prospective observational studies and the way we acquire data for them. Task Order #02, the SWAT study-Shock, Whole blood and Assessment of TBI, will provide the necessary outcome data to drive the use of whole blood for trauma resuscitation across the country."

Jason Sperry
University of Pittsburgh Department of Critical Care

LITES RESEARCH TASK ORDERS

TASK ORDER #01

Task Order #01 is a prospective observational study of trauma care including presentation characteristics, management practices and regional variation which may result in disparate outcomes that will inform future trials. The aims of Task Order #01 are (a) to characterize the epidemiology of moderated 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 March 2018, approximately 9,430 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. The linking of intensive pre-hospital and in-hospital granular data, while challenging, represents an innovative accomplishment which will promote further insight into trauma care and associated outcomes not available prior to this DOD Award.

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. Many patients with TBI have associated hemorrhagic shock, and there is clinical equipoise regarding the best approach to manage their blood pressure. Permissive hypotension may reduce blood loss but increase brain injury, while aggressive resuscitation may improve cerebral flow but worsen blood loss. Nearly all clinical trials of TBI exclude patients with severe blood loss; however, hemorrhagic blood loss often accompanies TBI. This clinical question has both military and civilian clinical significance. Recent innovation in the application of blood products in resuscitation has demonstrated that, when military trauma patients lose blood, their vascular volume should be replaced with products that recapitulate whole blood as closely as possible. With 1:1:1:1 (red blood cells: plasma: platelets: cryoprecipitate) and little to no crystalloid fluids, we have reached the limit of blood component therapy to approach the composition of fresh whole blood. However, this product has not been routinely used in the United States in the past 50 years, so studies of whole blood versus component therapy are absent from the literature and would significantly inform current and future battlefield transfusion protocols. The use of whole blood for early trauma resuscitation has been viewed by military trauma surgeons as the "essential next step" in the evolution of trauma resuscitation. 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: (1) 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 (2) 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 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.

Appendix A: FY92–FY17

Table A-1. Overview of Appropriations, Applications Received, and Awards Made for FY92-FY17

Programs Managed by CDMRP	Fiscal Year	Appropriations Received (in millions)	Applications Received	Applications Funded[1]
Alcohol and Substance Abuse Disorders[1]	2014-2017	$16.0	12	6
Amyotrophic Lateral Sclerosis	2007, 2009-2017	$69.4	494	62
Autism	2007-2017	$74.4	1,344	152
Bone Marrow Failure	2008-2017	$32.6	464	65
Breast Cancer	1992-2017	$3,381.3	55,876	6,778
Breast Cancer Research Semipostal[2]	1999-2017	$25.4		49
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	2011-2017	$23.2	160	29
Epilepsy	2015-2017	$22.5	103	24
Genetic Studies of Food Allergies	2009-2010	$4.4	60	9
Gulf War Illness	2006, 2008-2017	$149.0	506	167
Hearing Restoration	2017	$10.0	23	7
Institutionally Based Programs[1]	1995-2010	$486.3	306	501
Joint Warfighter Medical[1]	2012-2017	$254.0	137	72
Kidney Cancer	2017	$10.0	244	22
Lung Cancer	2009-2017	$113.5	2,912	222
Lupus	2017	$5.0	126	13
Military Burn[1]	2014-2017	$32.0	65	35
Multiple Sclerosis	2009-2017	$45.1	708	91
Myeloproliferative Disorders Research	2004	$4.3	18	9
National Prion Research Project	2002	$42.5	136	38
Neurofibromatosis	1996-2017	$317.9	1,555	385
Orthotics and Prosthetics Outcomes	2014-2017	$40.0	203	38
Osteoporosis	1995	$5.0	105	5
Ovarian Cancer	1997-2017	$296.5	3,723	427
Parkinson's[1]	2014-2017	$64.0	262	81
Peer Reviewed Alzheimer's[1]	2014-2017	$54.0	451	91
Peer Reviewed Cancer	2009-2017	$259.8	3,856	502
Peer Reviewed Medical	1999-2006, 2008-2017	$1,670.7	11,415	1,172
Peer Reviewed Orthopaedic	2009-2017	$338.5	1,246	255
Prostate Cancer	1997-2017	$1,620.0	18,453	3,267
Reconstructive Transplant	2015-2017	$39.0	403	67
Spinal Cord Injury	2009-2017	$217.9	1,032	219
Tick-Borne Disease	2016-2017	$10.0	99	13
Trauma Clinical Research Repository	2014	$5.0	2	1
Tuberous Sclerosis	2002-2006, 2008-2017	$71.0	685	147
Vision	2013-2017	$53.9	336	58
Miscellaneous				23

Continued on next page

Table A-1. Overview of Appropriations, Applications Received, and Awards Made for FY92-FY17 (cont.)

Programs Managed by CDMRP	Fiscal Year	Appropriations Received (in millions)	Applications Received	Applications Funded[1]
Additional Supported DOD Programs/Projects				
Armed Forces Institute of Regenerative Medicine II[3]	2017	$13.6		
Centers of Excellence	2015-2017	$17.2		1
Defense Medical Research and Development[4]	2010-2017	$712.0	1,984	508
Defense Medical Research and Development CSI Restoral[5]	2015-2017	$132.2		88
Psychological Health/Traumatic Brain Injury	2007, 2009-2017	$976.5	3,504	542
Rapid Innovation Fund	2011-2015	$35.7		15
Small Business Innovation Research/Small Business Technology Transfer	2014-2017	$51.4	121	175
Trauma Clinical	2016-2017	$20.0	0	0
Vision Prosthesis	2015-2016	$1.2		3
Other Submission Processes				
MRMC - BAA[6]			425	
Total		**$11,994.7**	**115,547**	**16,631**

[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; 0 fully funded and 2 partially funded.
[3] Armed Forces Institute of Regenerative Medicine II FY17 appropriations were used to fund 39 modifications.
[4] Includes 2013-2015 Clinical Research Intramural Initiative (CRII) and 2010 Chiropractic Clinical Trials.
[5] Includes 2016-2017 Clinical Research Intramural Initiative (CRII).
[6] CDMRP manages the application receipt and review process for the USAMRMC Broad Agency Announcement. Proposals that are funded are counted in the program that provided the funding. Of the 125 applications received, CDMRP funded 38.

Appendix B: FY17–FY18

Table B-1. FY2017-2018 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
2017	**$4.0M** for Alcohol and Substance Abuse Research	**Withholds** USAMRMC: $50,933 SBIR/STTR: $135,000 **Management Costs** $205,567 5.39%	**Research** Consortium Award: $3,608,500
	Total: $4.0M	**Total: $391,500**	**Total: $3,608,500**
2018	**$4.0M** for Alcohol and Substance Abuse Research	**Withholds** USAMRMC: $57,975 SBIR/STTR: $135,000 **Budgeted Management Costs** $265,000 7%	**Research** Budgeted Peer-Reviewed Research: $3,542,025
	Total: $4.0M	**Total: $457,975**	**Total: $3,542,025**

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

Table B-2. FY2017-2018 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
2017	**$7.5M** for Amyotrophic Lateral Sclerosis Research	**Withholds** USAMRMC: $95,110 SBIR/STTR: $252,000 **Management Costs** $473,880 6.63%	**Research** Therapeutic Idea Award: $5,117,398 Therapeutic Development Award: $1,561,612
	Total: $7.5M	**Total: $820,990**	**Total: $6,679,010**
2018	**$10M** for Amyotrophic Lateral Sclerosis Research	**Withholds** USAMRMC: $144,975 SBIR/STTR: $335,000 **Budgeted Management Costs** $620,025 7%	**Research** Budgeted Peer-Reviewed Research: $8,900,000
	Total: $10M	**Total: $1,100,000**	**Total: $8,900,000**

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

Table B-3. FY2017-2018 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
2017	**$7.5M** for Autism Research	**Withholds** USAMRMC: $108,720 SBIR/STTR: $252,000 **Management Costs** $491,894 6.89%	**Research** Idea Development: $2,805,216 Clinical Trial Award: $2,258,223 Clinical Translational Research: $1,583,947
	Total: $7.5M	**Total: $852,614**	**Total: $6,647,386**
2018	**$7.5 M** for Autism Research	**Withholds** USAMRMC: $108,720 SBIR/STTR: $252,000 **Budgeted Management Costs** $499,000 7%	**Research** Budgeted Peer-Reviewed Research: $6,640,280
	Total: $7.5M	**Total: $859,720**	**Total: $6,640,280**

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

Table B-4. FY2017-2018 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
2017	**$3.0M** for Bone Marrow Failure Research	**Withholds** USAMRMC: $43,198 SBIR/STTR: $100,000 **Management Costs** $844,128 29.55%	**Research** Idea Development Award - Early Career Investigator: $1,042,650 Idea Development Award - Established Investigator: $970,024
	Total: $3.0M	**Total: $987,326**	**Total: $2,012,674**
2018	**$3.0M** for Bone Marrow Failure Research	**Withholds** USAMRMC: $43,500 SBIR/STTR: $100,000 **Budgeted Management Costs** $199,955 7%	**Research** Budgeted Peer-Reviewed Research: $2,656,545
	Total: $3.0M	**Total: $343,455**	**Total: $2,656,545**

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

Table B-5. FY2017-2018 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
2017	**$120M** for Breast Cancer Research **$594,456** proceeds from the Stamp Out Breast Cancer Act	**Withholds** USAMRMC: $1,739,586 SBIR/STTR: $4,025,000 **Management Costs** $7,077,944 6.17%	**Research** Breakthrough Award Funding Level 1: $12,920,107 Breakthrough Award Funding Level 2: $27,938,035 Breakthrough Award Funding Level 3: $5,241,354 Breakthrough Award Funding Level 1 Partnering PI Option: $6,051,911 Breakthrough Award Funding Level 2 Partnering PI Option: $14,690,013 Breakthrough Award Funding Level 3 Partnering PI Option: $5,423,228 Breakthrough Award Funding Level 4 Clinical Trial-Partnering PI Option: $9,351,486 Breakthrough Fellowship Award: $5,745,401 Distinguished Investigator Award: $5,246,063 Era of Hope Scholar Award: $7,775,843 Innovator Award $7,368,485
	Total: $120,594,456	**Total: $12,842,530**	**Total: $107,751,926**
2018	**$120M** for Breast Cancer Research **$554,433** proceeds from the Stamp Out Breast Cancer Act	**Withholds** USAMRMC: $1,884,570 SBIR/STTR: $4,362,000 **Budgeted Management Costs** $8,627,000 7%	**Research** Budgeted Peer-Reviewed Research: $115,680,863
	Total: $120,205,848	**Total: $14,873,570**	**Total: $115,680,863**

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

Table B-6. FY2017-2018 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
2017	**$3.2M** for Duchenne Muscular Dystrophy Research	**Withholds** USAMRMC: $0 SBIR/STTR: $107,000 **Management Costs** $265,643 8.59%	**Research** Investigator Initiated Research: $1,927,357 Career Development Award: $900,000
	Total: $3.2M	**Total: $372,643**	**Total: $2,827,357**
2018	**$3.2M** for Duchenne Muscular Dystrophy Research	**Withholds** USAMRMC: $46,395 SBIR/STTR: $107,000 **Budgeted Management Costs** $213,000 7%	**Budgeted Research** Budgeted Peer-Reviewed Research: $2,833,605
	Total: $3.2M	**Total: $366,395**	**Total: $2,833,605**

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

Table B-7. FY2017-2018 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
2017	**$7.5M** for Epilepsy Research	**Withholds** USAMRMC: $108,591 SBIR/STTR: $252,000 **Management Costs** $253,051 3.54%	**Research** Idea Development Award - Funding Level 1: $780,401 Idea Development Award - Funding Level 2: $5,205,530 Epilepsy Risk Factors Award: $900,427
	Total: $7.5M	**Total: $613,642**	**Total: $6,886,358**
2018	**$7.5M** for Epilepsy Research	**Withholds** USAMRMC: $108,720 SBIR/STTR: $252,000 **Budgeted Management Costs** $439,280 6%	**Research** Budgeted Peer-Reviewed Research: $6,700,000
	Total: $7.5M	**Total: $800,000**	**Total: $6,700,000**

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

Table B-8. FY2017-2018 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
2017	**$20M** for Gulf War Illness Research	**Withholds** USAMRMC: $245,000 SBIR/STTR: $616,000 **Management Costs** $1,074,157 5.61%	**Research** Biorepository Resource Network Award: $3,278,756 Clinical Consortium Award: $5,333,082 Consortium Award: $264,126 Gulf War Illness Epidemiology Research Award: $513,514 Innovative Treatment Evaluation Award: $29,460 Investigator-Initiated Focused Research Award - Tier 1: $1,057,578 Investigator-Initiated Focused Research Award - Tier 2: $5,894,295 Investigator Initiated Research Award: $505,596 Investigator-Initiated Research Expansion Award - Collaborative Option: $54,500 New Investigator Award: $380,321 New Investigator Award - Transitioning Postdoctoral Fellow: $205,000 Qualitative Research Award: $548,615
	Total: $20M	**Total: $1,935,157**	**Total: $18,064,843**
2018	**$21M** for Gulf War Illness Research	**Withholds** USAMRMC: $304,980 SBIR/STTR: $668,000 **Budgeted Management Costs** $1,327,020 7%	**Research** Budgeted Peer-Reviewed Research: $18,700,000
	Total: $21M	**Total: $2,300,000**	**Total: $18,700,000**

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

Table B-9. FY2017-2018 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
2017	**$10M** for Hearing Restoration Research	**Withholds** USAMRMC: $144,615 SBIR/STTR: $335,000 **Budgeted Management Costs** $777,301 8.16%	**Research** Focused Research Award: $737,994 Translational Research Award: $8,005,090
	Total: $10M	**Total: $1,256,916**	**Total: $8,743,084**
2018	**$10M** for Hearing Restoration Research	**Withholds** USAMRMC: $335,000 SBIR/STTR: $144,975 **Budgeted Management Costs** $620,025 7%	**Research** Budgeted Peer-Reviewed Research: $8,900,000
	Total: $10M	**Total: $1,100,000**	**Total: $8,900,000**

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

Table B-10. FY2017-2018 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
2017	**$50M** for Joint Warfighter Medical Research	**Withholds** USAMRMC: $725,215 SBIR/STTR: $1,641,000 **Budgeted Management Costs** $2,012,878 4.03%	**Budgeted Research** Peer-Reviewed Research: $45,620,906
	Total: $50M	**Total: $4,379,094**	**Total: $45,620,906**
2018	**$50M** for Joint Warfighter Medical Research	**Withholds** USAMRMC: $725,610 SBIR/STTR: $1,626,000 **Budgeted Management Costs** $3,248,390 7%	**Budgeted Research** Budgeted Peer-Reviewed Research: $44,400,000
	Total: $50M	**Total: $5,600,000**	**Total: $44,400,000**

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

Table B-11. FY2017-2018 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
2017	**$10M** for Kidney Cancer Research	**Withholds** USAMRMC: $120,570 SBIR/STTR: $335,000 **Budgeted Management Costs** $662,058 6.94%	**Research** Concept Award: $1,024,515 Consortium Development Award: $999,996 Idea Development Award - Early Career Investigator: $2,312,474 Idea Development Award - Established Investigator: $2,448,245 Translational Research Partnership Award: $2,097,142
	Total: $10M	**Total: $1,117,628**	**Total: $8,882,372**
2018	**$15M** for Kidney Cancer Research	**Withholds** USAMRMC: $217,455 SBIR/STTR: $503,000 **Budgeted Management Costs** $999,000 7%	**Research** Budgeted Peer-Reviewed Research: $13,280,545
	Total: $15M	**Total: $1,719,455**	**Total: $13,280,545**

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

Table B-12. FY2017-2018 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
2017	**$12M** for Lung Cancer Research	**Withholds** USAMRMC: $153,460 SBIR/STTR: $403,000 **Management Costs** $673,009 5.88%	**Research** Concept Award: $2,052,844 Idea Development Award - Established Investigator: $1,588,710 Idea Development Award New Investigator: $1,082,711 Investigator-Initiated Translational Research Award: $3,201,231 Translational Research Partnership Award - Clinical Trial: $2,845,035
	Total: $12M	**Total: $1,229,469**	**Total: $10,770,531**
2018	**$14M** for Lung Cancer Research	**Withholds** USAMRMC: $202,950 SBIR/STTR: $470,000 **Budgeted Management Costs** $932,000 7%	**Research** Budgeted Peer-Reviewed Research: $12,395,050
	Total: $14M	**Total: $1,604,950**	**Total: $12,395,050**

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

Table B-13. FY2017-2018 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
2017	**$5M** for Lupus Research	**Withholds** USAMRMC: $48,729 SBIR/STTR: $168,000 **Budgeted Management Costs** $462,353 9.67%	**Research** Concept Award: $899,884 Impact Award: $3,421,034
	Total: $5M	**Total: $679,082**	**Total: $4,320,918**
2018	**$5M** for Lupus Research	**Withholds** USAMRMC: $72,480 SBIR/STTR: $168,000 **Budgeted Management Costs** $380,720 8%	**Research** Budgeted Peer-Reviewed Research: $4,378,800
	Total: $5M	**Total: $621,200**	**Total: $4,378,800**

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

Table B-14. FY2017-2018 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
2017	**$8M** for Military Burn Research	**Withholds** USAMRMC: $280,000 **Budgeted Management Costs** $55,801 0.72%	**Research** Broad Agency Announcement for Extramural Medical Research: $141,846 Burn Injuries Research Award - Funding Level 1: $159,050 Burn Injuries Research Award - Funding Level 2: $7,100 Clinical Study Award: $526,243 Clinical Trial Award - Research Level 1: $5,185,921 Clinical Trial Award - Research Level 2: $1,644,039
	Total: $8M	**Total: $335,801**	**Total: $7,664,199**
2018	**$8M** for Military Burn Research	**Withholds** USAMRMC: $280,000 **Budgeted Management Costs** $540,000 7%	**Research** Budgeted Peer-Reviewed Research: $7,180,000
	Total: $8M	**Total: $820,000**	**Total: $7,180,000**

The following abbreviations are used for withholds:
USAMRMC: US Army Medical Research and Materiel Command
Percent of management costs=management costs/(appropriation-withholds)

Table B-15. FY2017-2018 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
2017	**$6.0M** for Multiple Sclerosis Research	**Withholds** USAMRMC: $86,985 SBIR/STTR: $201,000 **Management Costs** $395,052 6.92%	**Research** Exploration - Hypothesis Development Award: $931,378 Investigator-Initiated Research Award: $4,385,585
	Total: $6M	**Total: $683,037**	**Total: $5,316,963**
2018	**$6.0M** for Multiple Sclerosis Research	**Withholds** USAMRMC: $86,985 SBIR/STTR: $201,000 **Budgeted Management Costs** $336,695 6%	**Research** Budgeted Peer-Reviewed Research: $5,375,320
	Total: $6M	**Total: $624,680**	**Total: $5,375,320**

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

Table B-16. FY2017-2018 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
2017	**$15M** for Neurofibromatosis Research	**Withholds** USAMRMC: $524,999 **Management Costs** $912,387 6.30%	**Research** Clinical Consortium Award: $2,265,367 Clinical Trial Award: $140,104 Exploration - Hypothesis Development Award: $1,104,305 Investigator-Initiated Research Award: $7,944,012 New Investigator Award: $2,108,826
	Total: $15M	**Total: $1,437,386**	**Total: $13,562,614**
2018	**$15M** for Neurofibromatosis Research	**Withholds** USAMRMC: $525,000 **Budgeted Management Costs** $1,013,000 7%	**Research** Budgeted Peer-Reviewed Research: $13,462,000
	Total: $15M	**Total: $1,538,000**	**Total: $13,462,000**

The following abbreviations are used for withholds:
USAMRMC: US Army Medical Research and Materiel Command
Percent of management costs=management costs/(appropriation-withholds)

Table B-17. FY2017-2018 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
2017	**$10M** for Orthotics and Prosthetics Outcomes Research	**Withholds** USAMRMC: $144,975 SBIR/STTR: $335,000 **Management Costs** $752,103 7.90%	**Research** Orthotics and Prosthetics Outcomes Research Award - Funding Level 1: $1,491,727 Orthotics and Prosthetics Outcomes Research Award - Funding Level 2: $7,276,195
	Total: $10M	**Total: $1,232,078**	**Total: $8,767,922**
2018	**$10M** for Orthotics and Prosthetics Outcomes Research	**Withholds** USAMRMC: $144,975 SBIR/STTR: $335,000 **Budgeted Management Costs** $665,025 7%	**Research** Budgeted Peer-Reviewed Research: $8,855,000
	Total: $10M	**Total: $1,145,000**	**Total: $8,855,000**

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

Table B-18. FY2017-2018 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
2017	**$20M** for Ovarian Cancer Research	**Withholds** USAMRMC: $289,935 SBIR/STTR: $671,000 **Management Costs** $1,275,316 6.70%	**Research** Clinical Development Award: $4,750,899 Clinical Development Award - Optional Nested Early Career Investigator: $2,029,924 Investigator-Initiated Research Award: $4,175,909 Outcomes Consortium Award: $812,648 Ovarian Cancer Academy - Early-Career Investigator Award: $2,123,445 Pilot Award - Early-Career Investigator Option: $1,492,097 Pilot Award - Established Investigator Option: $2,378,827
	Total: $20M	**Total: $2,236,251**	**Total: $17,763,749**
2018	**$20M** for Ovarian Cancer Research	**Withholds** USAMRMC: $289,935 SBIR/STTR: $671,000 **Budgeted Management Costs** $1,239,065 7%	**Research** Budgeted Peer-Reviewed Research: $17,800,000
	Total: $20M	**Total: $2,200,000**	**Total: $17,800,000**

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

Table B-19. FY2017-2018 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
2017	**$16M** for Parkinson's Research	**Withholds** USAMRMC: $448,865 **Management Costs** $2,127,284 13.68%	**Research** Early Investigator Research Award: $1,507,738 Focused Idea Award: $59,185 Investigator-Initiated Research Award: $6,861,451 Investigator-Initiated Research Award - Partnering PI Option: $4,995,477
	Total: $16M	**Total: $2,576,149**	**Total: $13,423,851**
2018	**$16M** for Parkinson's Research	**Withholds** USAMRMC: $560,000 **Budgeted Management Costs** $1,040,000 7%	**Research** Budgeted Peer-Reviewed Research: $14,400,000
	Total: $16M	**Total: $1,600,000**	**Total: $14,400,000**

The following abbreviations are used for withholds:
USAMRMC: US Army Medical Research and Materiel Command
Percent of management costs=management costs/(appropriation-withholds)

Table B-20. FY2017-2018 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
2017	**$15M** for Peer Reviewed Alzheimer's Research	**Withholds** USAMRMC: $217,455 SBIR/STTR: $503,000 **Management Costs** $635,624 4.45%	**Research** Convergence Science Research Award: $4,690,314 New Investigator Research Award: $1,652,711 Quality of Life Research Award: $799,905 Quality of Life Research Award - Clinical Trial: $65,063 Research Partnership Award: $6,435,928
	Total: $15M	**Total: $1,356,079**	**Total: $13,643,921**
2018	**$15M** for Peer Reviewed Alzheimer's Research	**Withholds** USAMRMC: $217,455 SBIR/STTR: $503,000 **Budgeted Management Costs** $979,545 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:
USAMRMC: US Army Medical Research and Materiel Command
SBIR/STTR: Small Business Innovation Research/Small Business Technology Transfer
Percent of management costs=management costs/(appropriation-withholds)

Table B-21. FY2017-2018 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
2017	**$60M** for Peer-Reviewed Cancer Research	**Withholds** USAMRMC: $1,041,218 SBIR/STTR: $2,013,000 **Management Costs** $3,667,010 6.44%	**Research** Bladder Cancer: $2,746,600 Brain Cancer: $2,830,071 Cancer in Children, Adolescents and Young Adults: $3,272,702 Colorectal Cancers: $8,881,343 Immunotherapy: $2,459,321 Listeria Vaccine for Cancer: $564,498 Liver Cancer: $4,947,169 Lymphoma: $2,800,774 Melanoma and Other Skin Cancers: $10,273,390 Mesothelioma: $1,572,520 Neuroblastoma: $2,309,161 Pancreatic Cancer: $4,016,689 Pediatric Brain Tumors: $4,177,742 Stomach Cancer: $2,426,792
	Total: $60M	**Total: $6,721,228**	**Total: $53,278,772**
2018	**$80M** for Peer-Reviewed Cancer Research	**Withholds** USAMRMC: $1,159,740 SBIR/STTR: $2,684,000 **Budgeted Management Costs** $5,330,000 7%	**Research** Budgeted Peer-Reviewed Research: $70,826,260
	Total: $80M	**Total: $9,173,740**	**Total: $70,826,260**

The following abbreviations are used for withholds:
USAMRMC: US Army Medical Research and Materiel Command
SBIR/STTR: Small Business Innovation Research/Small Business Technology Transfer
Percent of management costs=management costs/(appropriation-withholds)
FY2018 Peer Reviewed Cancer Research Program: The agreement provides $80,000,000 for a peer-reviewed cancer research program to research cancers not addressed in the breast, prostate, ovarian, kidney, and lung cancer research programs currently executed by the Department of Defense. The funds provided in the peer-reviewed cancer research program are directed to be used to conduct research in the following areas: adrenal cancer, bladder cancer, blood cancer, brain cancer, colorectal cancer, immunotherapy, listeria-based regimens for cancer, liver cancer, lymphoma, melanoma and other skin cancers, mesothelioma, myeloma, neuroblastoma, pancreatic cancer, pediatric brain tumors, stomach cancer, and cancer in children, adolescents and young adults.

Table B-22. FY2017-2018 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
2017	**$300M** for Peer-Reviewed Medical Research	**Withholds** USAMRMC: $4,350,563 SBIR/STTR: $9,954,000 **Management Costs** $10,816,439	**Research** Acute Lung Injury: $22,632,509 Antimicrobial Resistance: $20,319,156 Arthritis: $322,680 Chronic Migraine and Post-Traumatic Headache: $4,229,733 Congenital Heart Disease: $8,966,102 Diabetes: $8,135,099 Diarrheal Diseases: $914,765 Dystonia: $2,083,367 Eating Disorders: $5,430,246 Emerging Infectious Diseases: $12,469,330 Epidermolysis Bullosa: $9,245,141 Focal Segmental Glomerulosclerosis: $3,905,576 Fragile X: $1,715,744 Guillain-Barre Syndrome: $1,699,402 Hepatitis B and C: $3,371,932 Hydrocephalus: $2,320,750 Inflammatory Bowel Diseases: $641,786 Influenza: $15,693,659 Integrative Medicine: $23,194 Interstitial Cystitis: $3,550,850 Malaria: $8,161,563 Metals Toxicology: $304,668 Mitochondrial Disease: $6,523,009 Musculoskeletal Disorders: $3,909,038 Nanomaterials for Bone Regeneration: $8,020,206 Non-Opioid Pain Management: $7,349,385 Pancreatitis: $2,581,391 Polycystic Kidney Disease: $3,555,514 Post-Traumatic Osteoarthritis: $30,489,849 Pulmonary Fibrosis: $5,285,890 Respiratory Health: $12,304,955 Rett Syndrome: $322,000 Rheumatoid Arthritis: $1,816,920 Scleroderma: $3,858,150 Sleep Disorders: $4,838,965 Spinal Muscular Atrophy: $3,027,506 Sustained-Release Drug Delivery: $3,580,337 Tinnitus: $12,737,695 Tuberculosis: $5,225,004 Vaccine Development for Infectious Disease: $14,935,421 Vascular Malformations: $2,672,653 Women's Heart Disease: $5,707,858
	Total: $300M	**Total: $25,121,002**	**Total: $274,878,998**
2018	**$330M** for Peer-Reviewed Medical Research	**Withholds** USAMRMC: $4,785,585 SBIR/STTR: $10,961,000 **Budgeted Management Costs** $21,253,415 7%	**Research** Budgeted Peer-Reviewed Research: $293,000,000
	Total: $330M	**Total: $37,000,000**	**Total: $293,000,000**

The following abbreviations are used for withholds:
USAMRMC: US Army Medical Research and Materiel Command
SBIR/STTR: Small Business Innovation Research/Small Business Technology Transfer
Percent of management costs=management costs/(appropriation-withholds)
FY2018 Peer Reviewed Medical Research Program: The agreement provides $330,000,000 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, chronic pain management, congenital heart disease, constrictive bronchiolitis, diabetes, dystonia, eating disorders, emerging infectious diseases, endometriosis, epidermolysis bullosa, focal segmental glomerulosclerosis, Fragile X, frontotemporal degeneration, Guillain-Barre syndrome, hepatitis B and C, hereditary angiodema, hydrocephalus, immunomonitoring of intestinal transplants, inflammatory bowel diseases, interstitial cystitis, lung injury, malaria, metals toxicology, mitochondrial diseases, musculoskeletal disorders, myotonic dystrophy, non-opioid pain management, nutrition optimization, pancreatitis, pathogen-inactivated dried cryoprecipitate, post-traumatic osteoarthritis, pressure ulcers, pulmonary fibrosis, respiratory health, Rett syndrome, rheumatoid arthritis, scleroderma, sleep disorders, spinal muscular atrophy, sustained-release drug delivery, tinnitus, tissue regeneration, tuberculosis, vaccine development for infectious disease, vascular malformations, women's heart disease.

Table B-23. FY2017-2018 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
2017	**$30M** for Peer-Reviewed Orthopedic Research	**Withholds** USAMRMC: $434,863 SBIR/STTR: $1,006,000 **Management Costs** $1,571,425 5.50%	**Research** Applied Research Award: $7,447,897 Clinical Translational Research Award: $3,783,347 Clinical Trial Award: $6,597,918 Expansion Award: $3,982,662 Expansion Award - Research Level 2 - Clinical Trial: $996,860 Integrated Clinical Trial Award: $4,179,028
	Total: $30M	**Total: $3,012,288**	**Total: $26,987,712**
2018	**$30M** for Peer-Reviewed Orthopedic Research	**Withholds** USAMRMC: $433,116 SBIR/STTR: $1,006,000 **Budgeted Management Costs** $2,000,000 7%	**Research** Budgeted Peer-Reviewed Research: $26,560,884
	Total: $30M	**Total: $3,439,116**	**Total: $26,560,884**

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

Table B-24. FY2017-2018 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
2017	**$90M** for Prostate Cancer Research	**Withholds** USAMRMC: $1,304,565 SBIR/STTR: $3,019,000 **Management Costs** $5,897,910 6.88%	**Research** Clinical Consortium Award - Clinical Research Site: $884,172 Clinical Consortium Award - Coordinating Center with Clinical Research Site Option: $4,089,894 Clinical Consortium Research Site Award: $4,137,068 Early Investigator Research Award: $5,670,706 Health Disparity Research Award - Established Investigator: $5,688,152 Health Disparity Research Award - New Investigator: $833,859 Idea Development Award - Established Investigator - Partnering PI Option: $17,339,932 Idea Development Award - Established Investigator: $13,578,863 Idea Development Award - New Investigator Option: $4,467,567 Impact Award: $4,238,674 Impact Award - Partnering PI Option: $11,255,164 Physician Research Award: $3,561,521 Prostate Cancer Biospecimen Resource Site Award: $68,427 Prostate Cancer Pathology Resource Network Award: $3,668,735 Prostate Cancer Pathology Resource Network Award - Partnering PI Option: $295,791
	Total: $90M	**Total: $10,221,475**	**Total: $79,778,525**
2018	**$100M** for Prostate Cancer Research	**Withholds** USAMRMC: $1,449,675 SBIR/STTR: $3,355,000 **Budgeted Management Costs** $6,660,000 7%	**Research** Budgeted Peer-Reviewed Research: $88,535,325
	Total: $100M	**Total: $11,464,675**	**Total: $88,535,325**

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

Table B-25. FY2017-2018 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
2017	**$12M** for Reconstructive Transplant Research	**Withholds** USAMRMC: $173,955 SBIR/STTR: $403,000 **Management Costs** $556,629 4.87%	**Research** Concept Award: $805,769 Investigator-Initiated Research Award: $6,389,146 Qualitative Research Award: $3,671,501
	Total: $12M	**Total: $1,133,584**	**Total: $10,866,416**
2018	**$12M** for Reconstructive Transplant Research	**Withholds** USAMRMC: $173,955 SBIR/STTR: $403,000 **Budgeted Management Costs** $723,045 6%	**Research** Budgeted Peer-Reviewed Research: $10,700,000
	Total: $12M	**Total: $1,300,000**	**Total: $10,700,000**

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

Table B-26. FY2017-2018 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
2017	**$30M** for Spinal Cord Injury Research	**Withholds** USAMRMC: $434,910 SBIR/STTR: $1,006,000 **Management Costs** $1,251,823 4.38%	**Research** Clinical Research Development Award: $381,687 Clinical Trial Award: $9,887,576 Investigator-Initiated Research Award: $12,666,632 Qualitative Research Award: $638,085 Translational Research Award: $3,733,287
	Total: $30M	**Total: $2,692,733**	**Total: $27,307,267**
2018	**$30M** for Spinal Cord Injury Research	**Withholds** USAMRMC: $434,910 SBIR/STTR: $1,006,000 **Budgeted Management Costs** $1,999,000 7%	**Research** Budgeted Peer-Reviewed Research: $26,560,090
	Total: $30M	**Total: $3,439,910**	**Total: $26,560,090**

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

Table B-27. FY2017-2018 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
2017	**$5M** for Tick-Borne Disease Research	**Withholds** USAMRMC: $72,333 SBIR/STTR: $168,000 **Management Costs** $304,070 6.39%	**Research** Idea Award - Established Investigator: $531,690 Investigator Initiated Research Award: $3,923,908
	Total: $5M	**Total: $544,402**	**Total: $4,455,598**
2018	**$5M** for Tick-Borne Disease Research	**Withholds** USAMRMC: $72,480 SBIR/STTR: $168,000 **Budgeted Management Costs** $329,520 7%	**Research** Budgeted Peer-Reviewed Research: $4,430,000
	Total: $5M	**Total: $570,000**	**Total: $4,430,000**

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

Table B-28. FY2016-2017 Trauma Clinical 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
2016	**$10M** for Trauma Clinical Research	**Withholds** USAMRMC: $148,389 **Management Costs** $654,883 6.65%	**Research** Linking Investigations in Trauma & Emergency Services: $9,196,728
	Total: $10M	**Total: $803,272**	**Total: $9,196,728**
2017	**$10M** for Trauma Clinical Research	**Withholds** USAMRMC: $144,975 SBIR/STTR: $335,000 **Budgeted Management Costs** $665,025 7%	**Research** Budgeted Peer-Reviewed Research: $8,855,000
	Total: $10M	**Total: $1,145,000**	**Total: $8,855,000**

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

Table B-29. FY2017-2018 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
2017	**$6M** for Tuberous Sclerosis Complex Research	**Withholds** USAMRMC: $86,615 SBIR/STTR: $201,000 **Management Costs** $426,290 7.46%	**Research** Clinical Translational Research Award: $720,118 Exploration - Hypothesis Development Award: $254,539 Idea Development Award - Established Investigator: $2,176,869 Idea Development Award - New Investigator: $2,134,569
	Total: $6M	**Total: $713,905**	**Total: $5,286,095**
2018	**$6M** for Tuberous Sclerosis Complex Research	**Withholds** USAMRMC: $86,985 SBIR/STTR: $201,000 **Budgeted Management Costs** $299,000 5%	**Research** Budgeted Peer-Reviewed Research: $5,413,015
	Total: $6M	**Total: $586,985**	**Total: $5,413,015**

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

Table B-30. FY2017-2018 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
2017	**$15M** for Vision Research	**Withholds** USAMRMC: $217,188 SBIR/STTR: $503,000 **Management Costs** $448,840 3.14%	**Research** Clinical Trial Award: $5,212,377 Technology/Therapeutic Development Award: $8,618,596
	Total: $15M	**Total: $1,169,028**	**Total: $13,830,972**
2018	**$15M** for Vision Research	**Withholds** USAMRMC: $217,455 SBIR/STTR: $503,000 **Budgeted Management Costs** $979,545 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:
USAMRMC: US Army Medical Research and Materiel Command
SBIR/STTR: Small Business Innovation Research/Small Business Technology Transfer
Percent of management costs=management costs/(appropriation-withholds)

Table B-31. FY2017 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
2017	**$46.7M** for Defense Medical Research and Development from the Guidance for the Development of the Force Funding	**Management Costs** $2,999,497 6.42%	**Research** Clinical Research Intramural Initiative: $3,388,077 Medical Simulation and Information Sciences Awards: $2,779,254 Military Infectious Diseases Awards: $2,220,000 Military Operational Medicine Awards: $4,274,223 Combat Casualty Care Awards: $17,790,648 Clinical and Rehabilitative Medicine Awards: 10,144,232 Accelerating Innovation in Military Medicine Research Award: 3,127,100
	Total: $46.7M	**Total: $2,999,497**	**Total: $43,723,534**

Percent of management costs=management costs/CDMRP executed funds

Table B-32. FY2017 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
2017	**$112.4M** for Defense Medical Research and Development from the Guidance for the Development of the Force Funding	**Management Costs** $7,278,811 6.47%	**Research** Medical Simulation and Information Sciences Awards: $13,931,260 Military Infectious Diseases Awards: $3,847,002 Military Operational Medicine Awards: $13,079,317 Combat Casualty Care Awards: $43,065,147 Clinical and Rehabilitative Medicine Awards: $31,197,334 Accelerating Innovation in Military Medicine Research Award: $22,458
	Total: $112.4M	**Total: $7,278,811**	**Total: $105,120,061**

Percent of management costs=management costs/CDMRP executed funds

Table B-33. FY2017 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
2017	**$81.5M** for Psychological Health and Traumatic Brain Injury Research	**Management Costs** $6,124,168 8%	**Research** Broad Agency Announcement: $16,716,422 Broad Agency Announcement for Extramural Medical Research: $13,087,538 Clinical Trial Award: $793,983 Neurosensory and Rehabilitation Research Award - Applied Research Option: $4,000 Psychological Health Research Award - Partner PI Option: $280,000 Traumatic Brain Injury Endpoints Development Award: $4,109,805 Implementation Science: $8,265,060 Prolonged Field Care Research Award - Funding Level 2 - Preclinical Research: $4,386,506 Prolonged Field Care Research Award - Funding Level 1 - Preclinical Research: $3,137,858 Prolonged Field Care Research Award - Funding Level 1 - Clinical Research: $1,482,841 Cognitive Resilience and Readiness Research Award - Applied Research: $2,240,574 Traumatic Brain Injury/Post-Traumatic Stress Disorder - Clinical Trial Award: $184,903 Psychological Health and Traumatic Brain Injury: $185,104 Applied Psychological Health Award with Clinical Trial - Partnering Option: $814,367 Complex Traumatic Brain Injury Rehabilitation Research Award - Funding Level 2 - Clinical Trial: $13,149,366 Complex Traumatic Brain Injury Rehabilitation Research Award - Funding Level 1: $1,832,899 Complex Traumatic Brain Injury Rehabilitation Research Award - Funding Level 2: $3,168,655 Complex Traumatic Brain Injury Rehabilitation: $1,499,715 Applied Research and Advanced Technology Development Award: $15,097
	Total: $81.5M	**Total: $6,124,168**	**Total: $75,354,693**

Percent of management costs=management costs/CDMRP executed funds

Table B-34. FY2017 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
2017	**$13.6M** for Armed Forces Institute of Regenerative Medicine	**Management Costs**	**Research** Focus Area Research: $13,552,000
	Total: $13.6M		**Total: $13,552,000**

Percent of management costs=management costs/CDMRP executed funds

Table B-35. FY2017 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
2017	**$21.8M** for Small Business Innovation Research/ Small Business Technology Transfer Research	**Management Costs**	**Research** Small Business Innovation Research: $16,285,168 Small Business Technology Transfer: $5,501,561
	Total: $21.8M		**Total: $21,786,730**

Percent of management costs=management costs/CDMRP executed funds

Table B-36. FY2017 Centers of Excellence CDMRP Executed Funds,
Management Costs, and Execution of Investment Strategy

Fiscal Year	CDMRP Executed Funds	Management Costs	Investment Strategy
2017	**$3.5M** for Centers of Excellence	**Withholds** USAMRMC: $120,837 **Budgeted Management Costs** $260,873 8%	**Research** Broad Agency Announcement: $3,074,290
	Total: $3.5M	**Total: $381,710**	**Total: $3,074,290**

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

Appendix C: Breast Cancer Research Semipostal Awards FY99–FY17

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

[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 $216,085; 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.

Appendix D: Acronyms

AA.....Aplastic Anemia
AACR.....American Association for Cancer Research
AAV.....Adeno-Associated Virus
AD.....Alzheimer's Disease
ADNI.....Alzheimer's Disease Neuroimaging Initiative
ADRD.....Alzheimer's Disease and Related Dementia
ADT.....Androgen-Deprivation Therapy
AFIRM.....Armed Forces Institute of Regenerative Medicine
ALS.....Amyotrophic Lateral Sclerosis
ALSRP.....Amyotrophic Lateral Sclerosis Research Program
ALT.....Advanced Life Technologies
AM.....Additive Manufacturing
AM-ABA.....Adaptive, Modular Applied Behavior Analysis
AML.....Acute Myeloid Leukemia
AMR.....Antibody-Mediated Rejection
AR.....Androgen Receptor
ARC.....Advanced Research Core
ARDS.....Acute Respiratory Distress Syndrome
ARP.....Autism Research Program
ARS.....Alternative RNA Splicing
ASADRP.....Alcohol and Substance Abuse Disorders Research Program
ASD.....Autism Spectrum Disorder
ASUD.....Alcohol and Substance Use Disorders
AUC.....Appropriate Use Criteria
AUD.....Alcohol Use Disorder
B.....Billion
BAA.....Broad Agency Announcement
BADER.....Bridging Advanced Development for Exception Rehabilitation (Consortium)
BBRAIN.....Boston Biorepository, Recruitment, and Integrative Network
BCBT.....Brief Cognitive Behavioral Therapy
BCRP.....Breast Cancer Research Program
BCRS.....Breast Cancer Research Semipostal (Program)
BGUS.....β-Glucuronidase
BM.....Bone Marrow
BMF.....Bone Marrow Failure
BMFRP.....Bone Marrow Failure Research Program
BRCA1.....Breast Cancer 1
BRCA2.....Breast Cancer 2
CAP.....Consortium to Alleviate Post-Traumatic Stress Disorder
CARE.....Concussion Assessment, Research, and Education (Consortium)
CBLB.....Casitas B-Lineage Lymphoma B
CBT-IWeb.....Cognitive Behavior Therapy-Based Treatment for Insomnia
CCCRP.....Combat Casualty Care Research Program
CD.....Crohn's Disease
CDC.....Centers for Disease Control and Prevention
cDC.....Conventional Dendritic Cell
CDE.....Common Data Element
CDMRP.....Congressionally Directed Medical Research Programs
CEBPD.....CCAAT/Enhancer-Binding Protein Delta
CENC.....Chronic Effects of Neurotrauma Consortium
CET.....Cognitive Enhancement Therapy
CLL.....Chronic Lymphocytic Leukemia
CNS.....Central Nervous System
COA.....Clinical Outcome Assessment
CPG.....Clinical Practice Guideline
CRC.....Concussion Research Consortium
CRII.....Clinical Research Intramural Initiative
CRMRP.....Clinical and Rehabilitative Medicine Research Program
CRPC.....Castration-Resistant Prostate Cancer
CSC.....Clinical Study Core
CSF.....Cerebrospinal Fluid
CSI.....Congressional Special Interest
CT.....Computed Tomography
CURE.....Citizens United for Research in Epilepsy
CYP17A1.....Cytochrome P450 17A1
DARPA.....Defense Advanced Research Projects Agency
DC.....Dendritic Cell
DECAMP.....Detection of Early Lung Cancer Among Military Personnel (Consortium)
DHA.....Defense Health Agency
DHP.....Defense Health Program
DLS.....Daily Living Skills
DMD.....Duchenne Muscular Dystrophy
DMDRP.....Duchenne Muscular Dystrophy Research Program
DMRDP.....Defense Medical Research and Development Program
DOD.....Department of Defense
EACE.....Extremity Trauma and Amputation Center of Excellence

EAE ..... Encephalomyelitis
EB-COP ..... Evidence-Based Clinical Outcome Assessment
eBRAP ..... Electronic Biomedical Research Application Portal
ECI ..... Early Career Investigator
ECM ..... Extracellular Matrix
EGS ..... Electronic Grants System
EIBI ..... Early Intensive Behavioral Therapy
EMT ..... Epithelial to Mesenchymal Transition
EPA ..... Environmental Protection Agency
ERP ..... Epilepsy Research Program
ESF ..... Energy-Storing Foot
EST ..... Enriched Supportive Therapy
ETEC ..... Enterotoxigenic Escherichia Coli
FARA ..... Focused Applied Research Award
FASN ..... Fatty Acid Synthase
FDA ..... US Food and Drug Administration
FITBIR ... Federal Interagency Traumatic Brain Injury Research
Flt3L ..... FMS-Like Tyrosine Kinase 3 Ligand
FOXP3 ..... Forkhead Box P3
FTE ..... Fallopian Tube Epithelium
FY ..... Fiscal Year
GCSF ..... Granulocyte-Colony Stimulating Factor
GDNF ..... Glial Derived Neurotrophic Factor
GI ..... Gastrointestinal
GMP ..... Good Manufacturing Practice
GOG ..... Gynecology Oncology Group
GVHD ..... Graft-Versus-Host Disease
GWI ..... Gulf War Illness
GWIRP ..... Gulf War Illness Research Program
HDAC6 ..... Histone Deacetylase 6
HER2 ..... Human Epidermal Growth Factor Receptor 2
HGSC ..... High-Grade Serous Carcinoma
HHS ..... US Department of Health and Human Services
HIF ..... Hypoxia Inducible Factor
HIT ..... Health Information Technology
HLA-DR2a ..... Human Leukocyte Antigen-DR Isotype 2a
HPV ..... Human Papillomavirus
HRRP ..... Hearing Restoration Research Program
ICU ..... Intensive Care Unit
IDA ..... Idea Development Award
IHC ..... Immunohistochemistry
IIRA ..... Investigator-Initiated Research Award
IL-2 ..... Interleukin-2
ILAE ..... International League Against Epilepsy
IND ..... Investigational New Drug
IOM ..... Institute of Medicine
IRF8 ..... Interferon Regulator Factor 8
ITCH ..... Itchy E3 Ubiquitin Protein Ligase Homolog
ITN ..... Institute for Translational Neuroscience
JASPER ..... Joint Attention; Symbolic Play; Engagement, and Regulation
JPC ..... Joint Program Committee
JWMRP ..... Joint Warfighter Medical Research Program
KCRP ..... Kidney Cancer Research Program
LCRP ..... Lung Cancer Research Program
LITES ..... Linking Investigations in Trauma and Emergency Services
LRP ..... Lupus Research Program
LTS ..... Long-Term Survivors
M ..... Million
MBRP ..... Military Burn Research Program
MDD ..... Materiel Development Decision
MDS ..... Myelodysplastic Syndrome
MDSC ..... Myeloid-Derived Suppressor Cells
MEAB ..... Military External Advisory Board
MET ..... Mesenchymal to Epithelial Transition
METRC ..... Major Extremity Trauma and Rehabilitation Consortium (Formerly the Major Extremity Trauma Research Consortium)
MHS ..... Military Health System
MIDRP ..... Military Infectious Diseases Research Program
MOCOG .... Multidisciplinary Ovarian Cancer Outcomes Group
MOMRP ..... Military Operational Medicine Research Program
MRI ..... Magnetic Resonance Imaging
MS ..... Multiple Sclerosis
MSI ..... Microsatellite Instability
mSINGS ..... Microsatellite Instability by Next-Generation Sequencing
MSISRP ..... Medical Simulation and Information Sciences Research Program
MSRC ..... Military Suicide Research Consortium
MSRP ..... Multiple Sclerosis Research Program
mTBI ..... Mild Traumatic Brain Injury
MTF ..... Military Treatment Facility
NAC ..... N-Acetylcysteine
NAL ..... Noncanonical Agonist Ligands
NAM ..... National Academy of Medicine
NAPA ..... National Alzheimer's Project Act
NASA ..... National Aeronautics and Space Administration
NaV1.7 ..... Sodium Selective Voltage-Gated Ion Channel 1.7
NCAA ..... National Collegiate Athletic Association
NCI ..... National Cancer Institute
NDA ..... New Drug Application
NETPR ..... Neurotoxin Exposure Treatment Parkinson's Research
NF ..... Neurofibromatosis

NF1 ..... Neurofibromatosis Type 1
NF2 ..... Neurofibromatosis Type 2
NFCTC ..... Neurofibromatosis Clinical Trials Consortium
NFRP ..... Neurofibromatosis Research Program
NFκB ..... Nuclear Factor Kappa B
NIH ..... National Institutes of Health
NSAID ..... Nonsteroidal Anti-Inflammatory Drug
NSF ..... National Science Foundation
NT ..... Neurotypical
OASD(HA) ..... Office of the Assistant Secretary of Defense for Health Affairs
OCA ..... Ovarian Cancer Academy
OCCA ..... Ovarian Cancer Consortium Award
OCRCA ..... Orthopaedic Care and Rehabilitation Consortium Award
OCRP ..... Ovarian Cancer Research Program
OEF ..... Operation Enduring Freedom
OETRP ..... Orthopaedic Extremity Trauma Research Program
OIF ..... Operation Iraqi Freedom
OND ..... Operation New Dawn
OPC ..... Oligodendrocyte Precursor Cell
OPG ..... Optic Pathway Glioma
OPORP ..... Orthotics and Prosthetics Outcome Research Program
ORP ..... Office of Research Protections
OS ..... Oxidative Stress
PA ..... Program Announcement
PAD ..... Program Area Directorate
PASA ..... Pharmacotherapies for Alcohol and Substance Abuse (Consortium)
PCa ..... Prostate Cancer
PCBN ..... Prostate Cancer Biorepository Network
PCCTC ..... Prostate Cancer Clinical Trials Consortium
pCR ..... Pathological Complete Response
PCRP ..... Prostate Cancer Research Program
PD ..... Parkinson's Disease
PD1 ..... Programmed Cell Death Protein 1
PDX ..... Patient-Derived Xenograft
PERK ... Protein Kinase R-Like Endoplasmic Reticulum Kinase
PET ..... Positron Emission Tomography
PH ..... Psychological Health
PH/TBIRP ..... Psychological Health and Traumatic Brain Injury Research Program
PHF ..... Polyhydroxy Fullerene
PI ..... Principal Investigator
PI3KΔ ..... Phosphoinositide 3-Kinase Delta
PLIÉ ..... Preventing Loss of Independence Through Exercise
PMC ..... Pain Management Collaboratory
PNES ..... Psychogenic Non-Epileptic Seizures
PNS ..... Peripheral Nerve Stimulation
PPARγ ..... Peroxisome Proliferator Activator Receptor-γ
PRARP ..... Peer Reviewed Alzheimer's Research Program
pRBD ..... Probable Rapid Eye Movement Sleep Behavior Disorder
PRCRP ..... Peer Reviewed Cancer Research Program
PRMRP ..... Peer Reviewed Medical Research Program
PROMOTE ..... Prostate Cancer Medically Optimized Genome Enhanced Therapy
PRORP ..... Peer Reviewed Orthopaedic Research Program
PRP ..... Parkinson's Research Program
PTE ..... Post-Traumatic Epilepsy
PTSD ..... Post-Traumatic Stress Disorder
R&A ..... Review and Analysis
R&D ..... Research and Development
Rb1 ..... Retinoblastoma 1
RDT&E ..... Research, Development, Test, and Evaluation
RHERP ..... Radiation Health Effects Research Program
RMSF ..... Rocky Mountain Spotted Fever
ROC ..... Risk-On-A-Chip
RS-tDCS ..... Remotely Supervised Transcranial Direct Current Stimulation
RTI ..... Research Triangle Institute
RTRP ..... Reconstructive Transplant Research Program
SBIR ..... Small Business Innovative Research
SC ..... Stem Cell
SCI ..... Spinal Cord Injury
SCIRP ..... Spinal Cord Injury Research Program
SEER ..... Surveillance, Epidemiology, and End Results
STAR METRICS® ..... Science and Technology for America's Reinvestment Measuring the EffecTs of Research on Innovation, Competitiveness and Science
STIC ..... Serous Tubal Intraepithelial Carcinoma
STRONG STAR ..... South Texas Research Organizational Network Guiding Studies on Trauma and Resilience
STS ..... Short-Term Survivors
STTR ..... Small Business Technology Transfer
TAPTE ..... Team Approach to the Prevention and Treatment of Post-Traumatic Epilepsy
TBDRP ..... Tick-Borne Disease Research Program
TBI ..... Traumatic Brain Injury
TCMR ..... T Cell-Mediated Rejection
TCRP ..... Trauma Clinical Research Program
TDA ..... Therapeutic Development Award
TED ..... Traumatic Brain Injury Endpoints Development (Initiative)

TET1 ..... Ten-Eleven Translocation Protein 1
Th1 ..... T-Helper Type 1 Cell
TIA ..... Therapeutic Idea Award
TIL ..... Tumor Infiltrating Lymphocytes
TMEM ..... Tumor Microenvironments of Metastasis
TNF ..... Tumor Necrosis Factor
TRA ..... Translational Research Award
TRACK-TBI ..... Transforming Research and Clinical Knowledge in Traumatic Brain Injury
Tregs ..... T-Regulatory T Cells
TRL ..... Technology Readiness Level
TSC ..... Tuberous Sclerosis Complex
TSCRP ..... Tuberous Sclerosis Complex Research Program
TZD ..... Thiazolidinedione
USAISR ..... US Army Institute of Surgical Research
USAMMA ..... US Army Medical Materiel Agency
USAMRAA ..... US Army Medical Research Acquisition Activity
USAMRMC ..... US Army Medical Research and Materiel Command
USDA ..... US Department of Agriculture
USU ..... Uniformed Services University of the Health Sciences
UV ..... Ultraviolet
VA ..... US Department of Veterans Affairs
VCA ..... Vascularized Composite Allotransplantation
VRP ..... Vision Research Program
WRAIR ..... Walter Reed Army Institute of Research
XF ..... Crossover Foot
XIAP ..... X-Linked Inhibitor of Apoptosis
XPO1 ..... Nuclear Export Protein 1

For more information, visit: http://cdmrp.army.mil
or contact us at:
usarmy.detrick.medcom-cdmrp.mbx.cdmrp-public-affairs@mail.mil
301-619-7071
September 30, 2018