CDMRP
Department of Defense

# 2016 Congressionally Directed Medical Research Programs

## Annual Report





*U.S. Army Medical Research and Materiel Command*

## Letter from the Director

It is an honor to serve as the Director of the Congressionally Directed Medical Research Programs (CDMRP) over the past three years. For 23 years, we have funded innovative and impactful research through the combined efforts of our partners including Congress, the military, consumers, clinicians, scientists and CDMRP professionals. Today, 28 research programs are aimed at making scientific breakthroughs in cancer research, military medical research, and other disease- and injury-specific research.

In all of our endeavors, and specifically through this report, we believe in transparency in all of our processes. The 2016 Annual Report reflects the composite work of our partnerships. Our achievements can be attributed in part to our unwavering dedication to our mission while maintaining the flexibility to adapt to emerging priorities, implementing new programs and processes, and establishing new partnerships with other military and government agencies, consumer organizations, academia, and private industry.

We encourage you to read this report as you will learn about our history, funding profiles, the numbers and types of research projects awarded, specific highlights for each program, and the knowledge and material products, which are the fruits of these efforts. Although many challenges lie ahead, we rise to these challenges to transform healthcare for our Service Members, their families, our Veterans, and all who will be touched by our research programs.

Colonel Wanda L. Salzer, M.D., M.H.Sc.,
U.S. Air Force Medical Corps
Director, CDMRP

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# Department of Defense
# U.S. Army Medical Research and Materiel Command
# Congressionally Directed Medical Research Programs
# Annual Report
# September 30, 2016

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# Introduction

## History

The Congressionally Directed Medical Research Programs (CDMRP) is a global funding organization for cancer research, military medical research, and other disease- and injury-specific research. The CDMRP represents a unique partnership among the U.S. Congress, the military, and the public. The CDMRP implements the investment of core dollars (presidential budget) and congressionally directed dollars provided to fund groundbreaking, high-impact research.

The CDMRP is located within the Department of Defense (DoD) U.S. Army Medical Research and Materiel Command (USAMRMC). The mission of the USAMRMC 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 the USAMRMC under Military Partnerships on page 11). Since its first appropriation of congressional funding in fiscal year 1992 (FY92), the CDMRP has been responsible for managing more than $10.8 billion (B) in appropriations.

## Fiscal Year 2016

The CDMRP continued to grow in FY16 with increased congressional appropriations for certain programs and the addition of two new programs, the Tick-Borne Disease Research Program and Trauma Clinical Research Program. The growth of the CDMRP over the last 10 years is shown in **Figure 1**.

## 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

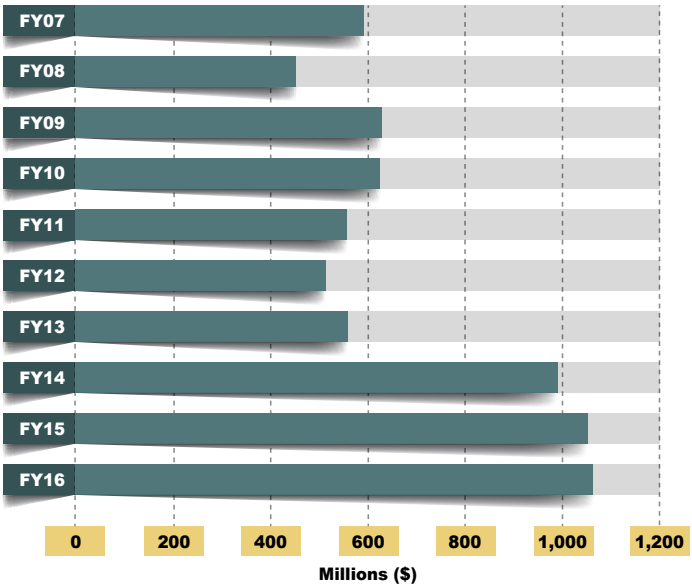



**Figure 1**. FY07–FY16 Research Funding

## Currently Funded Research Programs Include:

- Alcohol and Substance Abuse Disorders
- Amyotrophic Lateral Sclerosis
- Autism
- Bone Marrow Failure
- Breast Cancer
- Breast Cancer Research Semipostal
- Duchenne Muscular Dystrophy
- Epilepsy
- Gulf War Illness
- Joint Warfighter Medical
- Lung Cancer
- Military Burn
- Multiple Sclerosis
- Neurofibromatosis
- Orthotics and Prosthetics Outcomes
- Ovarian Cancer
- Parkinson's
- Peer Reviewed Alzheimer's
- Peer Reviewed Cancer
- Peer Reviewed Medical
- Peer Reviewed Orthopaedic
- Prostate Cancer
- Reconstructive Transplant
- Spinal Cord Injury
- Tick-Borne Disease
- Trauma Clinical
- Tuberous Sclerosis Complex
- Vision

## Major undertakings in FY16 are summarized on the following three pages

### *Institute of Medicine (IOM) Review*

Since its inception, the CDMRP has followed guidance from the IOM, now called the Health and Medicine Division (HMD) of the National Academies of Sciences, Engineering, and Medicine (NAS). The highly-regarded two-tiered program cycle employed by the CDMRP to review applications is based on recommendations from the IOM in 1993 (*Strategies for Managing the Breast Cancer Program: A Report to the U.S. Army Medical Research and Development Command*, 1993). The CDMRP has relied on the IOM's guidance to assess its processes beyond the 1993 report. In 1997 the IOM published *A Review of the DoD's Program for Breast Cancer Research*. In that report, the unique aspects of the Breast Cancer Research Program (BCRP) were called out, to include praise for the emphasis on consumer participation and the focus on innovation in research. Recommendations in the 1997 report were taken into consideration by the BCRP and other programs and were implemented where potential benefits and continued success could be identified. Since the 1993 and the 1997 reports by the IOM, the CDMRP has grown to include multiple different programs covering a wide range of diseases, injuries, or conditions.

As required by Senate Appropriations Committee Report Number 113-211, an important FY16 development for the CDMRP is an assessment by the IOM, now HMD, of the two-tiered review process and coordination of research priorities with the National Institutes of Health (NIH) in order to identify how well the processes are working and whether they may be improved. In order for the CDMRP to continue to succeed across programs, a review by the HMD presents a great opportunity for assessment of the CDMRP's processes by a distinguished panel of experts convened by the HMD. Although the HMD is contracted to prepare this assessment by the Defense Health Agency (DHA), the CDMRP has actively engaged with the HMD, offering presentations, written responses to questions, and participation in an open discourse with the HMD panel during the assessment period. In addition to the review of the two-tiered program cycle, the HMD panel will also assess the coordination of the CDMRP with the NIH and the U.S. Department of Veterans Affairs (VA). A full report from the HMD on the CDMRP two-tiered review process and coordination efforts is expected to be published by the end of 2016.

### *The CDMRP Website*

The CDMRP website is an important means to disseminate information to the public, the scientific community, and all CDMRP stakeholders. In FY15, the CDMRP completed the merger of the research management support activities previously performed by the Telemedicine and Advanced Technology Research Center into the CDMRP's research management operations. With this merger, the CDMRP greatly expanded the number of programs it is managing; therefore, an evaluation of the utility and effectiveness of the existing website was undertaken, and an extensive effort was begun to redesign the site. A diverse team reviewed the existing content and brainstormed new and fresh ideas. Keeping in mind the different audiences and functionality needed, the team assessed the strengths and weaknesses of the site, including content, navigation, graphics, and animation. Other sites were examined to get ideas about the latest in web design, and new concepts began to emerge. A redesign was developed and tested, and in January 2016, the newly designed CDMRP website was launched.


**The redesign more effectively answers our audiences' needs, provides new and easily understood information, and engages visitors.**

## *Electronic Biomedical Research Application Portal (eBRAP)*

eBRAP and Electronic Grants System (EGS) provide critical capabilities not supported through Grants.gov. eBRAP and EGS support multiple organizations for the processing and management of DoD medical research grants.

eBRAP is a research pre-application and full application receipt, processing, and management tool that supports the mission of the DHA, USAMRMC, U.S. Army Medical Research Acquisition Activity (USAMRAA), and CDMRP. In response to 171 FY14 and FY15 funding opportunities, eBRAP received and processed 21,141 pre-applications and 11,753 full applications.

eBRAP:

- Is the front-end interface for bilateral communication with the research community, and provides worldwide web-based accessibility for receipt and processing of pre-applications and 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
- Directly accepts DoD intramural applications
- Interfaces directly with Grants.gov for retrieval, processing, and administrative review of extramural applications
- Uses computer-automated processes associated with Program Announcement release, as well as batch retrieval, processing, modification, and compliance review
- Provides capability to allow researchers to review and modify application components (following submission to Grants.gov)
- Provides capability to communicate with the research community on a one-to-one basis and in batches
- Is responsive to Contracting, Human Use, and Animal Use regulations

## *Electronic Grants System (EGS)*

EGS is a business system that is designed to focus on activities related to management of funded awards for the entire life cycle from negotiations to closeout, allowing multiple organizations to collaborate in a virtual workspace.

- EGS enables real-time electronic workflows among offices of the USAMRMC, including USAMRAA, Office of Surety, Safety and Environment and Office of Research Protections.
- Multiple user groups are able to collaborate allowing for data inputs, running reports and managing daily administrative tasks associated with research award management in a central, secure location.
- Integrated processes including award management, program management, financial management and program evaluation are incorporated into EGS to create a seamless solution to enable efficiencies.
- System-to-system interfaces allow for transfer of data between MRMC and DoD partner organizations.

## Our Programs

**Highlights of FY15–FY16 programs managed and/or supported by the CDMRP can be found within the program pages in this Annual Report, beginning on page 29. As detailed in Table 1 (on page 5), the CDMRP successfully completed obligation of FY15 appropriations across 26 programs encompassing 918 new research awards. In addition, in FY16, the CDMRP initiated the management of $1,065 million (M) across 28 programs.**

- Research outcomes and findings are captured and categorized in customized modules for analysis for program evaluation efforts, interaction with funded investigators, and reporting to stakeholders.
- Award data in EGS is made public nightly via a connection to the CDMRP website in which users can view abstracts of projects and a listing publications as they become available.
- Use of EGS has expanded to include management of DoD Intramural awards managed by several Joint Program Committees and other MRMC agencies.
- Recent enhancements allow for the Office of Research Protections 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 FederalReporter.

### *Federal RePORTER*

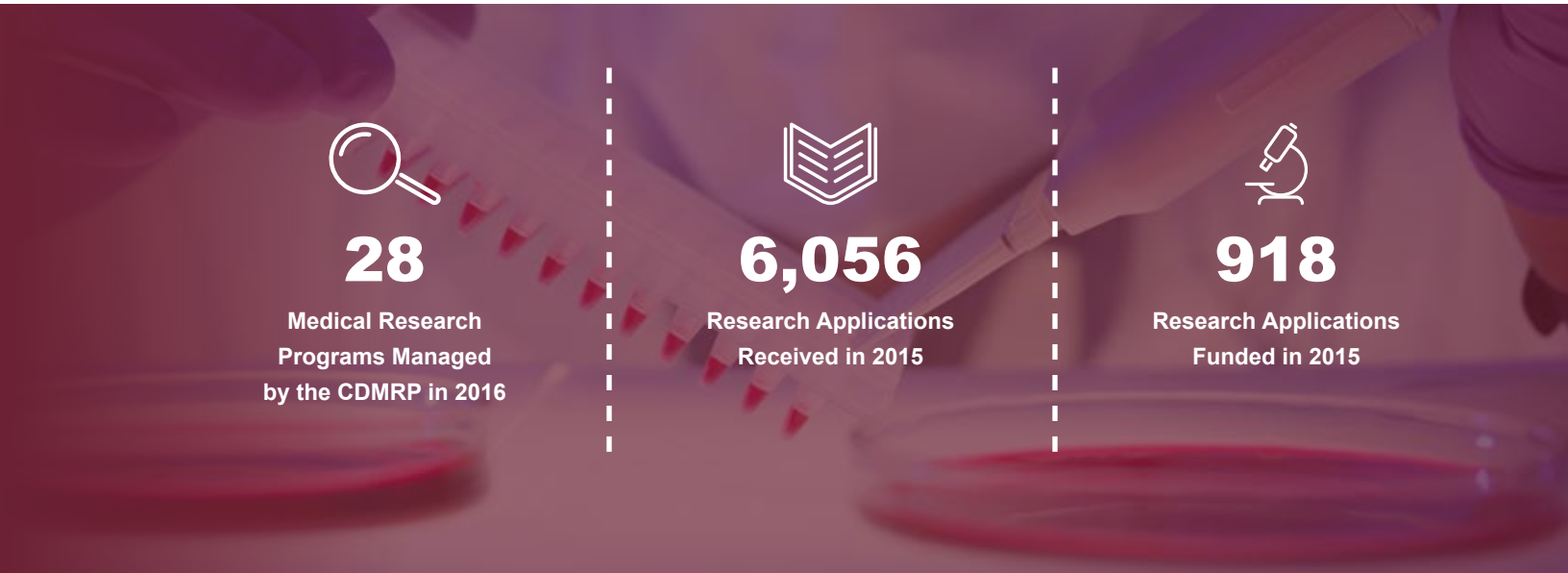
In response to U.S. Government Accountability Office recommendations, the CDMRP continued its efforts to support government transparency by participating in the STAR METRICS Federal RePORTER initiative (http://federalreporter.nih.gov), which consolidates award data from several agencies, including the Department of Health and Human Services (HHS), the Department of Agriculture, the DoD, the National Science Foundation, the VA, the Environmental Protection Agency, and the National Aeronautics and Space Administration. This initiative allows multiple agencies to house award data in a central database. Although separate from the NIH RePORTER, the Federal RePORTER utilizes some of its basic functions on a core set of data required from all agencies, allowing analysis and comparison. 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. CDMRP-funded awards from FY08 onwards are currently included in the Federal RePORTER system, and new awards will be posted by the end of each fiscal year.

***All of the programs managed by the CDMRP share the common goal of advancing research solutions that will lead to cures or enhancements in patient care.***

**Table 1**. CDMRP Programs, Appropriations, and Applications Received and Awarded in FY15–FY16

| Research Programs Managed by the CDMRP | FY15 | | | | FY16 | |
|---|---|---|---|---|---|---|
| | Funds Received (in millions) | Applications Received | Applications Funded | Funding Modifications Completed | Funds Received (in millions) | Applications Received to Date |
| Alcohol and Substance Abuse Disorders[1] | $4.0 | n/a | - | 2 | $4.0 | TBD |
| Amyotrophic Lateral Sclerosis | $7.5 | 41 | 10 | - | $7.5 | 39 |
| Autism | $6.0 | 58 | 7 | - | $7.5 | 71 |
| Bone Marrow Failure | $3.2 | 35 | 5 | - | $3.0 | 28 |
| Breast Cancer | $120.0 | 1,627 | 116 | - | $120.0 | 982 |
| Breast Cancer Research Semipostal[2] | $0.5 | n/a | - | 2 | $0.2 | n/a |
| Duchenne Muscular Dystrophy | $3.2 | 27 | 5 | - | $3.2 | TBD |
| Epilepsy | $7.5 | 25 | 5 | - | $7.5 | TBD |
| Gulf War Illness | $20.0 | 74 | 26 | 2 | $20.0 | TBD |
| Joint Warfighter Medical[3] | $50.0 | 11 | 12 | 18 | $50.0 | 32 |
| Lung Cancer | $10.5 | 329 | 29 | 1 | $12.0 | 298 |
| Military Burn | $8.0 | 36 | 7 | 4 | $8.0 | TBD |
| Multiple Sclerosis | $5.0 | 40 | 6 | - | $6.0 | 53 |
| Neurofibromatosis | $15.0 | 67 | 21 | - | $15.0 | 51 |
| Orthotics and Prosthetics Outcomes | $10.0 | 62 | 7 | - | $10.0 | TBD |
| Ovarian Cancer | $20.0 | 234 | 26 | - | $20.0 | 204 |
| Parkinson's | $16.0 | 23 | 7 | 4 | $16.0 | TBD |
| Peer Reviewed Alzheimer's | $12.0 | 75 | 16 | - | $15.0 | TBD |
| Peer Reviewed Cancer | $50.0 | 560 | 110 | - | $50.0 | 456 |
| Peer Reviewed Medical | $247.5 | 1,294 | 166 | 7 | $278.7 | 445 |
| Peer Reviewed Orthopaedic | $30.0 | 57 | 10 | 1 | $30.0 | TBD |
| Prostate Cancer | $80.0 | 697 | 118 | 14 | $80.0 | 282 |
| Reconstructive Transplant | $15.0 | 94 | 25 | 1 | $12.0 | TBD |
| Spinal Cord Injury | $30.0 | 90 | 18 | - | $30.0 | 113 |
| Tick-Borne Disease | n/a | n/a | n/a | n/a | $5.0 | TBD |
| Trauma Clinical | n/a | n/a | n/a | n/a | $10.0 | TBD |
| Tuberous Sclerosis | $6.0 | 43 | 11 | 1 | $6.0 | 54 |
| Vision | $10.0 | 78 | 7 | - | $10.0 | TBD |
| **Additional Supported DoD Programs/Projects** | | | | | | |
| Centers of Excellence | $10.7 | n/a | 1 | 3 | $3.1 | TBD |
| Defense Medical Research and Development | $103.4 | 174 | 45 | 105 | $120.5 | 267 |
| Defense Medical Research and Development CSI Restoral | $53.9 | n/a | 35 | 23 | $31.6 | TBD |
| Psychological Health/Traumatic Brain Injury | $82.6 | 25 | 31 | 24 | $69.6 | 18 |
| Rapid Innovation Fund | $5.0 | n/a | 2 | - | TBD | TBD |
| Small Business Innovation Research/ Small Business Technology Transfer | $11.2 | 36 | 31 | 7 | $3.6 | 10 |
| Vision Prosthesis | $1.0 | n/a | 3 | - | TBD | TBD |
| **Other Submission Processes** | | | | | | |
| MRMC - Broad Agency Announcement[4] | | 144 | | | | 158 |
| **Total** | **$1,054.7** | **6,056** | **918** | **219** | **$1,065.0** | **3,561** |

(1) Proposals received in FY14 were funded with FY14 and FY15 funds.
(2) Breast Cancer Semipostal funds applications received and reviewed by the BCRP.
(3) Joint Warfighter Medical Execution Management Breakdown: 9 awards and 10 mods managed by CDMRP; 3 awards and 5 mods managed by USAMMDA; and 3 mods managed by USAMMA.
(4) CDMRP manages the application receipt and review process for the USAMRMC Broad Agency Announcement. Funded proposals that are managed by CDMRP counted in the program that provided the funding. Of the 144 applications received, CDMRP funded 51.



**28**
**Medical Research Programs Managed by the CDMRP in 2016**

**6,056**
**Research Applications Received in 2015**

**918**
**Research Applications Funded in 2015**

# Our Management Cycle

The CDMRP has always employed a 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. Programs follow the management cycle described in detail on the following pages, but they do so with consideration of the requirements and needs of each program's stakeholders. Each step in the management cycle is depicted in **Figure 2** and discussed in detail in this section.

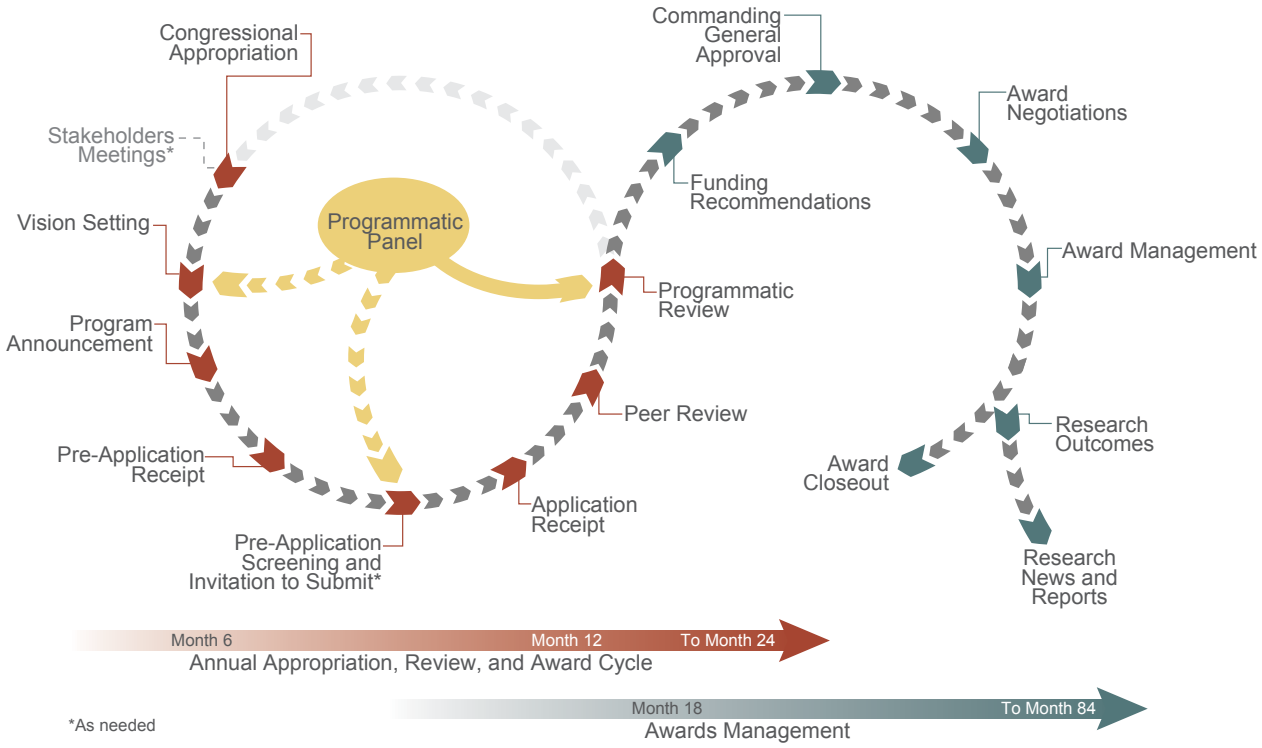



**Figure 2**. Program Management Cycle

## Funding Process

**The CDMRP is funded through the DoD 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 the 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 the CDMRP are added every year during the budget approval cycle by members of the House or Senate, in response to requests by consumers and disease survivors.**

## 1. Core Dollars, Congressional Appropriation, and Receipt of Funds

Funds for programs are a direct response to the needs of Service Members and their families, research communities, and the public at large. The congressionally appropriated programs are added annually to the DoD appropriation. The Defense Health Program (DHP) also includes funds for military medical research from the President's budget (core dollars). Over the years, the CDMRP has been one of the main organizations within the USAMRMC to serve as a research execution manager for these funds.

## 2. Stakeholders Meeting

For new programs, a stakeholders meeting is held to survey the research landscape and identify gaps in both the scientific and consumer interest areas. Stakeholders are world-renowned consumers, scientists, and clinicians. Recommendations from the stakeholders meeting are used to facilitate vision setting.

## 3. Vision Setting

A vision setting meeting is held to define an annual investment strategy for a given program. The development of an annual investment strategy is based on the recommendations of the NAS HMD. The purpose of an annual vision setting meeting is to discuss the current landscape of the disease, condition, or injury; identify scientific and clinical research gaps; and develop a strategy to fill these gaps. The process of vision setting brings together experts in science, the clinic, and the military, as well as consumers, to determine the program's goals and award mechanisms to be offered by the program. Based on the discussions, the vision setting process concludes with development of an investment strategy for the program's available funds. PAs/funding opportunities are developed to support the most needed areas of scientific research for the program year.

## 4. Program Announcements (PAs) and Broad Agency Announcements (BAAs)

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

## 5. Applicant Submission and Receipt

For all of the award mechanisms, application submission requires a multistep process consisting of a pre-application submission (which includes a letter of intent or a pre-proposal) followed by full application submission. Pre-proposals are an abbreviated submission outlining the research aims, strategy, innovation, and/or impact of the project. Pre-proposals may be screened by either the programmatic reviewers or a scientific peer review panel, based on the requirements described in each PA or BAA. The final product of the screening is a recommended list of invited applicants. As summarized in **Table 2**, in FY16, the CDMRP received 8,873 pre-proposals that, after screening and invitation, resulted in 2,995 full applications received. In

**Table 2.** Number of Submissions Received October 1, 2015–September 30, 2016, across FY15–FY16 Programs

| Mechanism Submissions | |
|---|---|
| Pre-proposals screened | 8,873 |
| Letters of intent received | 3,364 |
| Total pre-applications received | 12,237 |
| **Full Application Submissions** | |
| Full applications from invitations only | 2,995 |
| Full applications from letters of intent | 2,894 |
| Total full applications received | 5,889 |

addition, the CDMRP received 2,894 full applications from mechanisms that required a letter of intent, for a total of 5,889 full applications received in this fiscal year.

On October 1, 2014, the 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 the USAMRMC. These areas of interests are determined annually by the USAMRMC Program Area Directorates (PADs) in response to evolving research priorities and knowledge gaps. For FY16, 400 pre-applications and 158 full applications were submitted to the BAA process and forwarded to the USAMRMC PADs for programmatic decisions.

## 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 includes both scientific 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 that 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.

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

**Programmatic Review:** After applications have been peer reviewed, they go through a criteria-based programmatic review by experts including scientists, clinicians, military members, and/or laypersons. At the programmatic review level, the panel uses the criteria published in the funding opportunity (PA or BAA) in a comparison-based assessment that includes programmatic relevance, portfolio balance, and scientific merit and makes recommendations for funding. To ensure impartiality and the integrity of the process, programmatic reviewers are prohibited from applying for funds for the fiscal year in which they participated in vision setting.

## 7. Approval of the Awards List

After the process of programmatic review, a funding list is generated that is reviewed and approved by the appropriate authority, the Commanding General, the USAMRMC, and/or the DHA, Research and Development (R&D) Directorate, within the Office of the Assistant Secretary of Defense for Health Affairs (OASD[HA]). Upon approval, electronic notification is sent to program applicants to inform them of their funding status.

### *Multistep Process to Minimize Award Duplication and Overlap*


**1** List of past, current, and pending funding support submitted by the Principal Investigator at the time of application submission

**2** Screen for duplicate submissions during compliance checks

**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)

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

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

**6** 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

## 8. Award Negotiations and Management

Negotiation and management of awards are a major focus of the USAMRMC offices and organizations, including the CDMRP, USAMRAA, and Office of Research Protections. During the period of performance for awards (which can be up to 4 years), the CDMRP actively manages and monitors progress. The awards management process is depicted in **Figure 3**. Over the past 5 years, an average of 700 new awards was made each fiscal year. As of September 30, 2016, the CDMRP has managed 14,829 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 for the lifetime of the award. The Science Officer also acts as a liaison, maintaining the proper flow of information between the awardee institution, the Principal Investigator (PI), the CDMRP, and offices within the USAMRMC. Technical analysis of the budget with respect to the scope of work to be performed is completed to maximize savings and avoid overlap in research funding with other funded projects. Once all aspects of negotiation are complete, an award is signed, and an assistance agreement (grant or cooperative agreement) or contract is issued. A CDMRP Grants Officer's Representative or Contracting Officer's Representative is assigned to each respective award and serves as the technical point of contact for the Contracting Officer. The life-cycle management of awards continues throughout the period of performance with monitoring of the technical progress, regulatory review, financial reporting, and 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 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 entire period of performance.

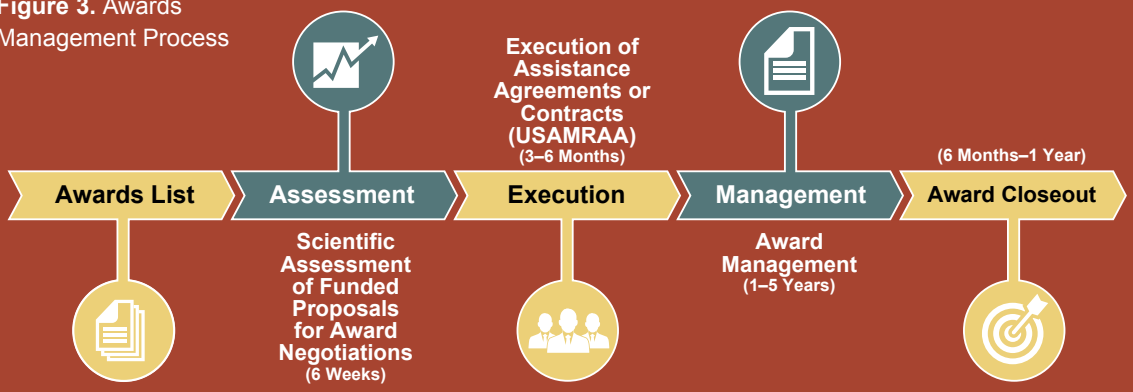
## 9. Award Closeout

Award closeout takes place at both the USAMRAA and the CDMRP and is usually performed 6 months after the period of performance has expired. During this time, the CDMRP carefully reviews the final progress report and the patent report, while the 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 the CDMRP's EGS.

## 10. Research News and Reports/Public Relations

To be transparent to the public, various communication processes and social media techniques are used to share information with stakeholders and audiences. The newly designed 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, 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 the CDMRP to expand information dissemination strategies include YouTube (http://www.youtube.com/user/CDMRP) and Twitter (https://twitter.com/CDMRP); in addition, the CDMRP maintains an e-mail listserve of more than 85,000 unique recipients.

**Figure 3.** Awards Management Process



# Vital Partnerships

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

## Consumers

The CDMRP has been a catalyst for the inclusion of consumers (patients, survivors, family members, and/or caregivers) in the review of research applications as full voting members. Consumers first served as reviewers for the CDMRP at the programmatic review level in 1993, and their role was soon expanded to scientific peer review in 1995. The CDMRP has developed a model of consumer inclusion that has been adopted by other funding agencies. Consumers are nominated to scientific peer review panels by the lay organizations. Similar to scientific peer review panels, consumers also serve at the programmatic review level of the CDMRP. In each tier of review, consumers serve alongside scientists, clinicians, and leading experts, and all have an equal voice and vote in deliberations. 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. Throughout the growth of the CDMRP, consumers and stakeholders remain the foundation for many of the programs executed and managed by the CDMRP. For more information on consumer involvement, see the consumer involvement pages on the CDMRP website (http://cdmrp.army.mil).

## The Scientific Community

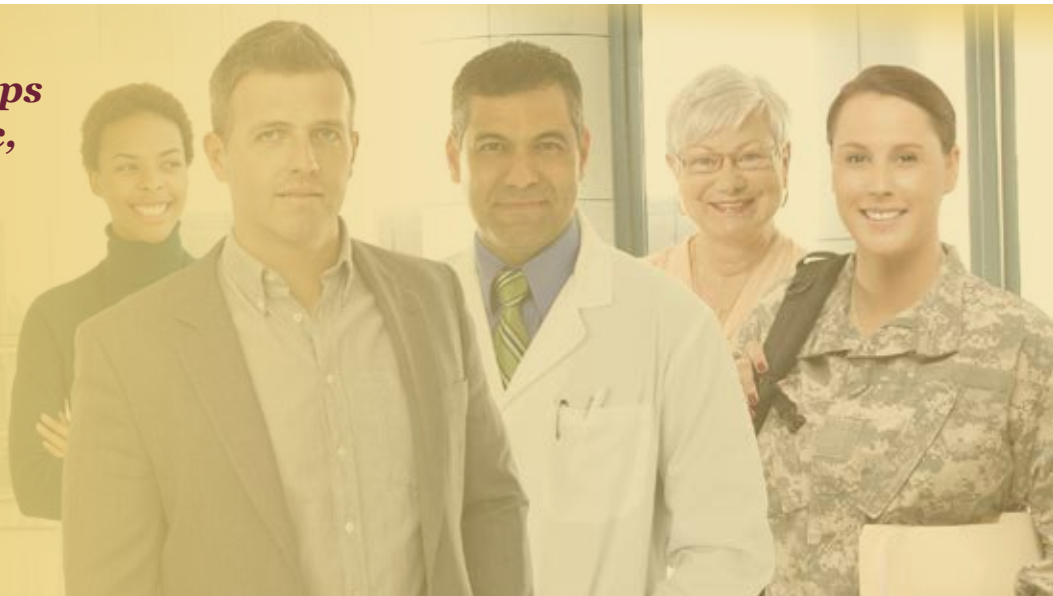
The scientific community has been an integral partner in assisting the CDMRP to shape the future of healthcare. They serve on the two-tier review of applications; research the complex causes of diseases, conditions, and injuries; and translate this knowledge into improved prevention, treatment interventions, 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 reviewed.

***In FY16, nearly 575 consumers served on CDMRP peer review panels, and over 75 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 FY16, nearly 3,075 scientists and clinicians provided necessary subject matter expertise on peer review panels, and over 525 scientists and clinicians served as programmatic reviewers. As of September 30, 2016, over 200 scientists, clinicians, and consumers have served as ad hoc programmatic reviewers. Since its inception, approximately 10,739 researchers have been funded by the CDMRP to improve the health and quality of life of all people.***

***The CDMRP's partnerships with consumer, scientific, professional, and military communities are at the core of the management process.***



## Military Partnerships

### *U.S. Army Medical Research and Materiel Command*

**Vision:** Lead the advancement of military medicine

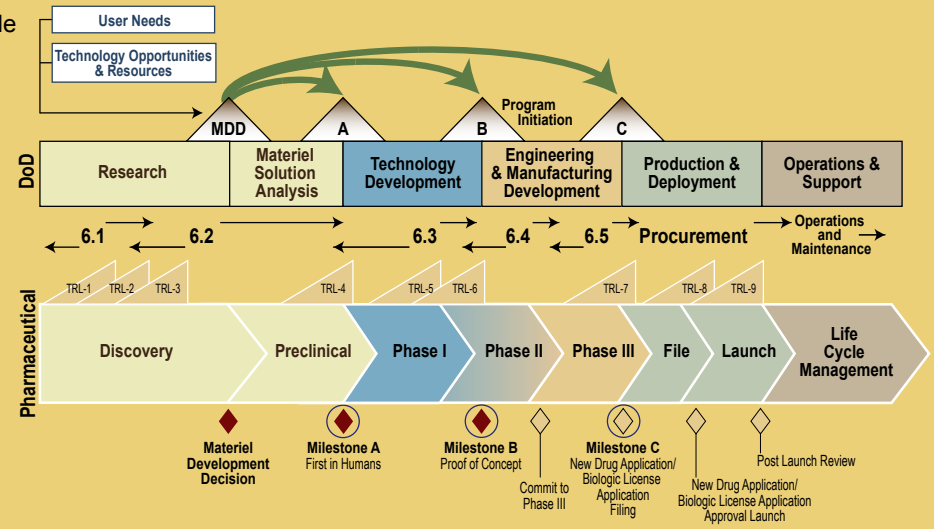
**Mission:** Responsively and responsibly create, develop, deliver, and sustain medical capabilities for the Warfighter

The CDMRP is located within the USAMRMC, the largest medical research organization within the DoD. The USAMRMC is responsible for managing medical research programs that address both military and civilian beneficiaries. The USAMRMC motto, "Protect, Project, Sustain," underscores its support of the Warfighter through ensuring that Service Members are protected from disease and treated for injuries or conditions. The 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 the 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. The 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**.

Many of the research projects managed by the CDMRP have the potential to become fielded products for our Warfighters. The 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, U.S. Food and Drug Administration (FDA) regulations, and best industry practices, and it allows the USAMRMC to remain responsive to the changing needs of the Warfighter. Projects funded through the 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, the 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 the 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. Once in Decision Gate, product development will be guided by an Integrated Product Team. Science Officers from the 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,


**Figure 4.** The USAMRMC Team

**Figure 5.** Decision Gate Life Cycle



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 the USAMRMC's commitment to remain a good steward of taxpayer dollars and a world-class medical research and development organization.

## *Defense Health Agency Research, Development and Acquisition Directorate*

The DHA is a joint, integrated Combat Support Agency that reports to the Office of the 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 R&D Directorate was established within the 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. As directed by the OASD(HA), the DHA R&D Directorate manages and executes the DHP Research, Development, Test, and Evaluation appropriation. The DHP congressional and core programs managed or supported by the CDMRP are overseen by the R&D Directorate, which works closely with the CDMRP to provide:

- Centralized oversight of research and development 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

**Vision:** Advance collaborative, innovative medical research and development to improve military community health and save lives on and off the battlefield

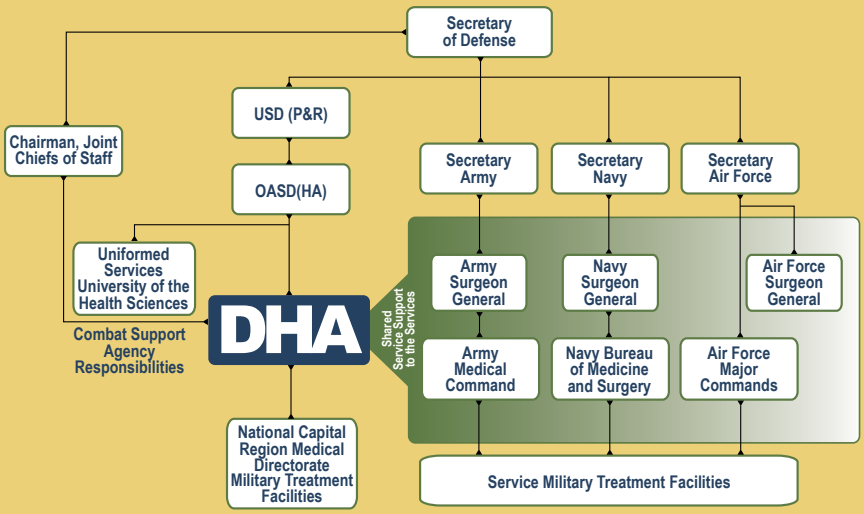
**Mission:** Implement best practices to responsibly design, prioritize and integrate medical research, development and acquisition programs across the continuum of care. By fostering strategic partnerships and transitioning medical discoveries to deployable products, R&D will enhance the readiness and resilience of the military community

The DHA R&D Directorate organizes annual focused Review & Analysis (R&A) meetings to facilitate short-term and long-term planning of research within and across core medical research and development portfolios. These R&A meetings bring together senior leadership from across different military and government agencies (DoD, VA, NIH) to give them visibility of the research, help identify program needs and issues, and provide a forum for feedback and guidance. While historically held only for core research and related portfolios, 16 additional CDMRP-assigned congressional programs were presented at R&A meetings for the first time in FY16. 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 (JPCs)*

The JPCs are DHA R&D Directorate advisory bodies composed of medical and military experts that provide guidance on funding recommendations and program management support for DHA R&D Directorate-funded research. The JPCs advise and work through the USAMRMC PADs, which provide strategic oversight of this research.

**Figure 6.** DHA Reporting and Support Structure




The DHA reports to the OASD(HA) and provides support to the three Military Services.

- JPC-1: Medical Simulation & Information Sciences
- JPC-2: Military Infectious Diseases
- JPC-5: Military Operational Medicine
- JPC-6: Combat Casualty Care
- JPC-7: Radiation Health Effects
- JPC-8: Clinical & Rehabilitative Medicine

The CDMRP provides management support to the JPCs/PADs for DHP core research program areas. The combined effort leverages the 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 R&D mission. The CDMRP administers these programs as the Defense Medical Research and Development Program (DMRDP). The 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 their families. (For additional information about the DMRDP and other programs/projects supported by the CDMRP, see pages 90–97 in this report). In FY16, the 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 the CDMRP's vision of transforming healthcare for Service Members and the American public through innovative and impactful research.

### *U.S. 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. The 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 panels, and the CDMRP funds VA investigators for both individual and collaborative research efforts. To date, more than 200 investigators at VA institutions have been funded by the CDMRP.

As one prime example, the 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 46–47 for additional details on the 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 the 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 and the Chronic Effects of Neurotrauma Consortium (CENC), which are described in further detail on pages 16–17 of this Annual Report.

This year, the CDMRP also worked with the VA to provide input and share information in support of the Veteran Engagement Initiative in VA Research, specifically as related to the integration of consumers into the review process and participation in research projects. In addition to individual staff meetings, the CDMRP was invited to present a live, nationwide VA Health Services Research & Development Cyberseminar that described the CDMRP's history and unique features, with a focus on highlighting how consumers are intricately involved in every aspect of the CDMRP's program management cycle.

***These partnerships are invaluable to the CDMRP's vision of finding and funding the best research to support the Warfighter and the American public.***

# 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 ongoing consortia are provided in the following sections.*

## Alzheimer's Disease Neuroimaging Initiative (ADNI)

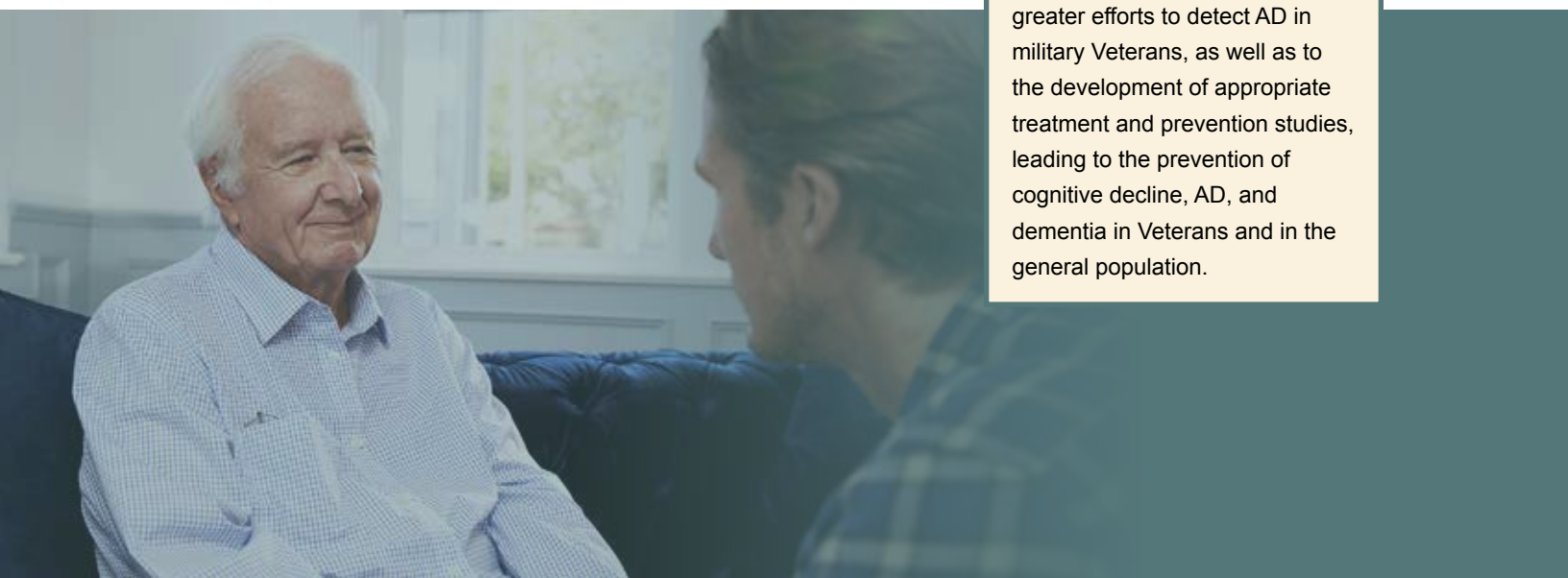
The purpose of the DoD ADNI is to examine the possible connections between TBI and PTSD, as well as the signs and symptoms of Alzheimer's disease (AD) on Veterans as they age. TBI and PTSD are highly prevalent consequences of military service and combat. Medical attention has focused on the acute treatment of these conditions; however, long-term consequences may be greater than the immediate morbidity in terms of human suffering, economic cost, and pain to families. Three studies supported by the ADNI will help determine the extent to which TBI and PTSD are risk factors for the development of dementia due to AD or other factors:

- Effects of Traumatic Brain Injury and Post-Traumatic Stress Disorder on Alzheimer's Disease in Veterans Using Imaging and Biomarkers in the Alzheimer's Disease Neuroimaging Initiative
- Effects of Traumatic Brain Injury and Post-Traumatic Stress Disorder on Alzheimer's Disease in Veterans with Mild Cognitive Impairment Using the Alzheimer's Disease Neuroimaging Initiative
- Effects of Traumatic Brain Injury and Post-Traumatic Stress Disorder and Alzheimer's Disease on Brain Tau in Vietnam Veterans Using the Alzheimer's Disease Neuroimaging Initiative

Military and VA records are used to identify Vietnam War Veterans with either: (1) evidence of ongoing PTSD; (2) a well-documented history of moderate or severe TBI (this group includes those who have both PTSD and a TBI); or (3) comparable Veteran controls. The initial study enrolled subjects who met criteria for normal cognition. The study was later expanded to include these same three cohorts, but include subjects who also meet criteria for mild cognitive impairment. All subjects are contacted by mail/telephone and pre-screened for eligibility. Evidence of current and lifetime PTSD is determined by the Structured Diagnostic Interview for DSM-IV and the Clinician Administered PTSD Scale. Subjects meeting criteria for one of the three cohorts (with or without minimal cognitive impairment) are referred to one

***ADNI***

Results from these studies are expected to lead directly to greater efforts to detect AD in military Veterans, as well as to the development of appropriate treatment and prevention studies, leading to the prevention of cognitive decline, AD, and dementia in Veterans and in the general population.



of 19 selected ADNI clinics for clinical examination; cognitive tests; amyloid positron emission tomography (PET) using F18 Florbetapir; magnetic resonance imaging (MRI) (structural, diffusion tensor, and resting state BOLD functional MRI); lumbar puncture for cerebrospinal fluid; markers of tau, P tau, and amyloid beta; and blood for genetics. After 1 year, the clinical/cognitive battery and MRI are repeated. The objective is to detect an increase in AD markers (measured with PET, MRI, and cerebrospinal fluid biomarkers, as well as cognitive testing) associated with history of TBI or ongoing PTSD. Because considerable evidence suggests that, while brain Aβ might precipitate cognitive decline in aging, the actual severity of the decline is more closely linked to deposition of brain tau. Therefore, the study was again expanded to determine the effects of prior TBI and ongoing PTSD on brain tau and the longitudinal change of brain tau measured with the tau-specific ligand 18F-AV-1451([F-18] T807) and PET scanning. Vietnam Veteran subjects already enrolled in either of the first two studies are invited to enroll in the third study and receive the additional PET scan. A separate cohort of civilian subjects, currently enrolled in the ADNI2, is also invited to participate. Read more about the ADNI at http://www.adni-info.org/.

## Armed Forces Institute of Regenerative Medicine (AFIRM)

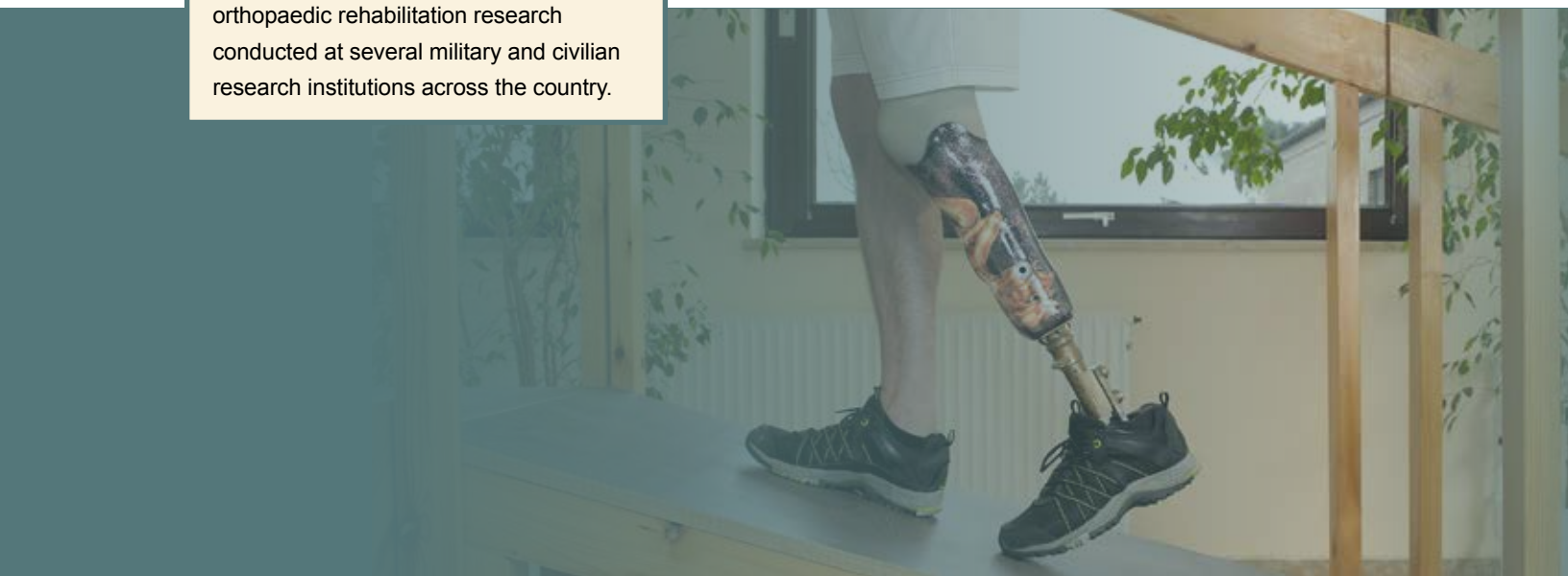
The AFIRM was established in 2008 through a partnership among the USAMRMC, Office of Naval Research, U.S. Air Force Office of the Surgeon General, NIH, and Veterans Health Administration of the VA. AFIRM was initially composed of two independent civilian research consortia: the Rutgers – Cleveland Clinic Consortium and the Wake Forest – Pittsburgh Consortium, both of whom worked closely with the U.S. Army Institute of Surgical Research at Fort Sam Houston, Texas. In 2013, with the period of performance winding down on the original agreements, funding for AFIRM II was made available by the same partners. The Wake Forest–led Warrior Restoration Consortium (WRC) was selected for this next phase of AFIRM. The WRC includes members from both of the initial AFIRM consortia, along with new investigators. In all, the WRC consists of over 30 member institutions. The research of the AFIRM is currently divided into five focus areas representing critical clinical challenges that need advanced solutions for Wounded Warriors: Extremity Regeneration, Craniomaxillofacial Regeneration, Skin Regeneration, Composite Tissue Allotransplantation and Immunomodulation, and Genitourinary/Lower Abdomen Reconstruction. Each focus area addresses the major tissues affected by trauma. The research addresses both restoring and regenerating tissue at the component and complex integrated structure levels. The goals of the research programs are to restore not only form and cosmetic appearance to the injured areas, but also to provide full functional recovery.

## Bridging Advanced Developments for Exceptional Rehabilitation (BADER) Consortium

Clinical trials addressing lower-extremity trauma are currently aimed at improving step-to-step control during walking, analyzing the benefits of powered ankle prostheses for amputees with differing levels of mobility, and maximizing outpatient rehabilitation effectiveness. Consortium projects focused on prosthetic devices strive to determine the optimal height and stiffness of a running-specific leg

***BADER***

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.



prosthesis, as well as to characterize the response of prosthetic feet to applied loads and impacts representative of military tasks and the effects of such loads upon gait. A clinical study to examine functional outcome measures for individuals with upper-extremity trauma is also included.

## The Chronic Effects of Neurotrauma Consortium (CENC)

The CENC is a joint DoD and VA effort dedicated to establishing a comprehensive understanding of the chronic sequelae associated with neurotrauma, primarily focused on 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. Currently, CENC leverages collaborations with over 30 participating institutions across academia, industry, the DoD, and the VA. Studies under way include efforts in the area of epidemiology, neurosensory co-morbidities, neuroimaging standardization, and follow-up from studies initiated in-theater. 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/.

***CENC***

The Consortium 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 (CARE) Consortium

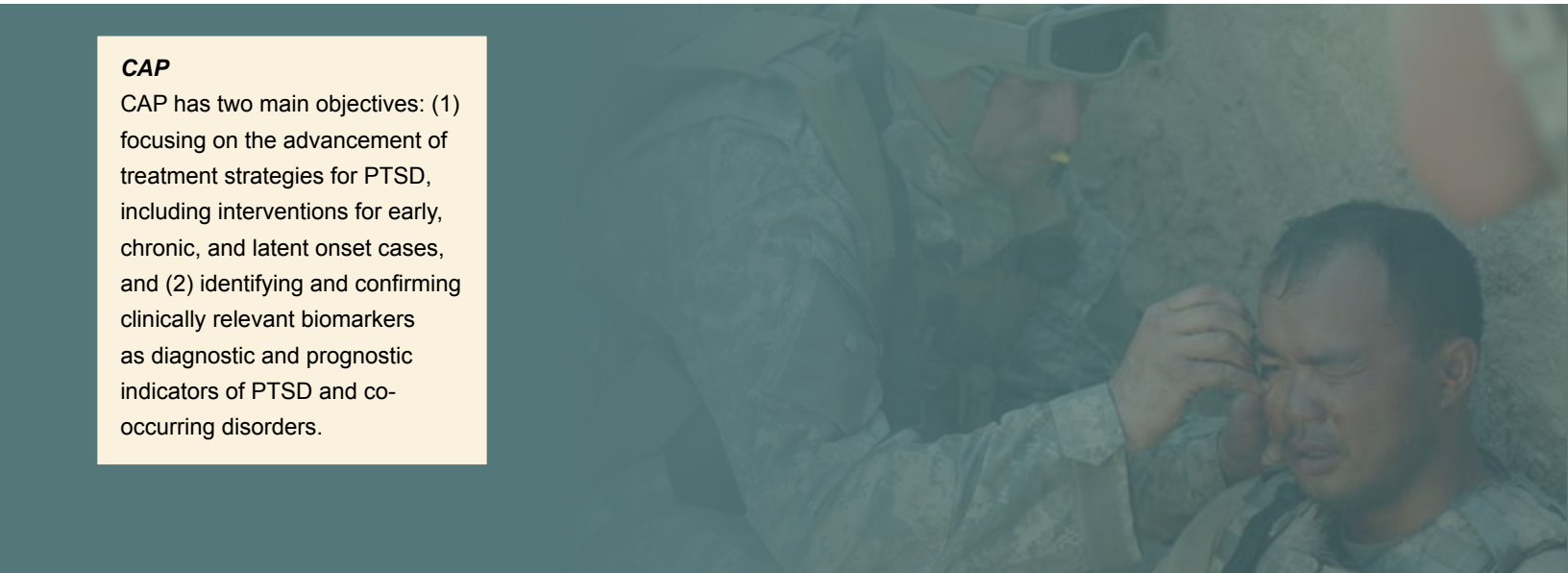
The National Collegiate Athletic Association (NCAA)–DoD Grand Alliance CARE Consortium is a joint DoD and NCAA research effort dedicated to studying the natural history of sport-related concussion in order to better understand the development of and trajectory of recovery from concussion. Since its inception in 2014, the 3-year consortium project has enrolled more than 25,000 student athletes and cadets at 30 performance sites (26 NCAA universities and 4 service academies). As of September 2016, the study team has captured about 1,300 concussions, one-third of which were captured at the service academies. The CARE Consortium, and the data the team 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 Federal Interagency Traumatic Brain Injury Research informatics system and will be released to the public at project completion. The CARE team is led by Dr. Tom McAllister at Indiana University and includes a Clinical Study Core at the University of Michigan and an Advanced Research Core at the Medical College of Wisconsin. Initial results from the study are expected to be published in 2017. More information can be found at http://careconsortium.net/.

## The Consortium to Alleviate Post-Traumatic Stress Disorder (CAP)

The 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. Research within the CAP focuses across a range of topics, including behavioral health disorders, mood and anxiety disorders, sexual dysfunction, neurologic disorders, pain, cognitive deficits, and neuroendocrine

***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.



deficits. The CAP is led by Consortium Director Dr. Alan Peterson of the University of Texas Health Science Center San Antonio and the South Texas Veterans Health Care System, and Co-Director Dr. Terry Keane of the VA Boston Healthcare System, who is also Director of the Behavioral Science division of the National Center for PTSD. The CAP coordinating center is responsible for the 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, and Duke University. In addition, the CAP has funded the following 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 the following: a Randomized Clinical Trial for Cognitive-Behavioral Therapy for Post-Traumatic Headache and the Clinical Trial of Ketamine for Antidepressant Resistant PTSD. Numerous VA, academic, and military institutions across the United States participate in CAP. Additional information can be found at https://tango.uthscsa.edu/consortiumtoalleviateptsd/.

## Detection of Early Lung Cancer Among Military Personnel Consortium

The Detection of Early Lung Cancer Among Military Personnel Consortium is designed to develop and 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, four military treatment facilities, 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 will handle the clinical trial infrastructure, protocol development, clinical trial data management, quality assurance, regulatory compliance, imaging analysis, and site management. Two projects have been initiated 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 scan; 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.

## Gulf War Illness Consortium

The Gulf War Illness Consortium is led by Dr. Kimberly Sullivan of Boston University and brings together established GWI researchers across the nation to investigate the pathobiological mechanisms responsible for GWI symptoms as they relate to brain-immune interactions. This Consortium has initiated a series of clinical and preclinical studies to specifically identify brain-immune pathways that can be targeted for intervention by a variety of glial-modulating 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.

***Gulf War Illness Consortium***

Results from this integrated approach should lead to a rational and efficient basis for identifying diagnostic markers and beneficial treatments for GWI.

## Institute for Translational Neuroscience (ITN)

The ITN, a Consortium comprised of 18 institutions, was established with congressionally directed funding in 2010 to address the growing concern regarding alcohol and substance use disorders within the military and civilian populations. Now in its fifth year of operation, the ITN has formed a unique and promising strategy to accelerate the development of novel therapeutics for substance use disorders. The scientific objectives of the ITN are: (1) to identify molecular mechanisms, targets, and candidate compounds; (2) to determine the efficacy of the candidate compound(s) in vitro and in vivo (animal models); (3) to conduct proof-of-principle, pilot-scale clinical experiments or trials; and (4) to rapidly translate findings into full-scale clinical experiments/trials. To facilitate the transition from bench to bedside, a Translational Coordinating Core was established to attract collaborations with outside sources, such as the 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.

***ITN***

Thus far, 18 unique clinical and pre-clinical studies have been successfully awarded and supported through the Consortium. Ten awards are still active, and two are planned for FY16. More information regarding three of these studies and their results can be found at http://cdmrp.army.mil/asadrp/research_highlights/15mitchell_highlight.shtml.

## Major Extremity Trauma Research Consortium (METRC)

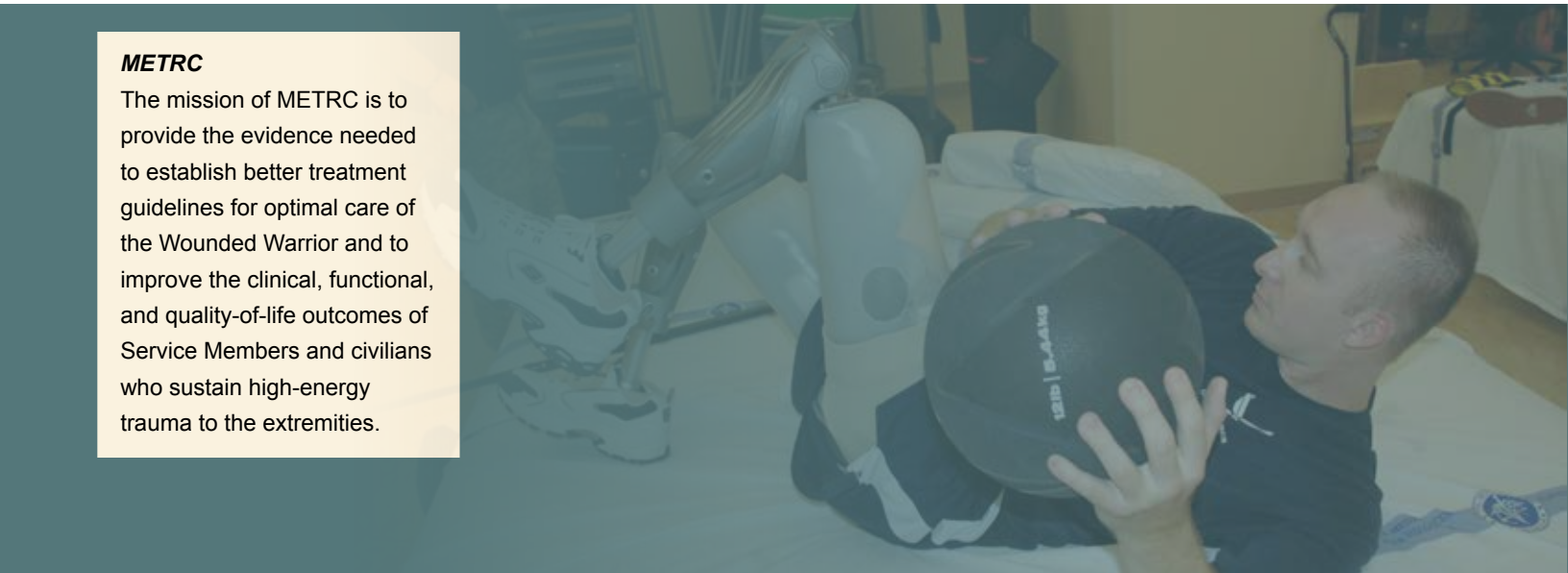
METRC1 was funded by a previous Orthopaedic Extremity Trauma Research Program Award; METRC2 was established in 2010 with congressionally directed funding. The CDMRP assumed management of the METRC2 studies in 2015. The coordinating center for METRC studies is located at the Johns Hopkins Bloomberg School of Public Health. This center collaborates with four military treatment facilities, 22 civilian study sites, and over 40 satellite centers to conduct five core METRC2 studies, in addition to several other ancillary studies. Led by Dr. Ellen MacKenzie of Johns Hopkins University and Dr. Michael Bosse at Carolinas Medical Center, the core METRC2 studies include:

- OUTLET: Comparing patient outcomes post limb salvage and amputation among patients with severe foot and ankle injuries
- TAOS: Comparing outcomes in patients undergoing transtibial amputation with or without tibia-fibula synostosis
- PACS: Developing a novel tool to aid clinicians in timely and accurate diagnoses of acute compartment syndrome
- PAIN: Evaluating multimodal approaches for peri-operative pain management in treatment of lower limb fractures
- TCCS: Implementing a collaborative care intervention to address patients' psychosocial needs and improve health-related quality of life

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

***METRC***

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



## Military Suicide Research Consortium (MSRC)

The DoD has funded a number of studies proposing to investigate methods to better identify who is at risk for, and to decrease the likelihood of, suicidal behavior. The Denver Research Institute and Florida State University received funding from the Military Operational Medicine Research Program in FY08 to create the MSRC, with the goal of integrating and synchronizing DoD and civilian efforts to implement a multidisciplinary approach to suicide prevention. Additional funding was provided in FY16 in order to continue the MSRC for 5 more years. These awards, which are managed by the MSRC, are led by Drs. Peter Gutierrez and Thomas Joiner.

***MSRC***
The MSRC-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.

To date, 25 studies have been funded by the MSRC, in addition to several Postdoctoral Pilot Projects and Dissertation Completion Awards. These studies are being conducted at numerous VA and military installations across the country and cover a broad spectrum of the research continuum, ranging from etiological to prevention/screening and treatment. Populations being studied include Service Members, Veterans, and family members of Service Members and Veterans. Additional studies will be funded over the next few years.

The MSRC has developed a database to capture Common Data Elements collected in each of the funded studies. 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.

Six 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.

## Neurofibromatosis Clinical Trials Consortium (NFCTC)

The NFCTC (http://www.uab.edu/nfconsortium) was established by the DoD Neurofibromatosis Research Program in 2006 to develop and perform clinical trials for the treatment of neurofibromatosis (NF) complications in children and adults. The NFCTC was subsequently funded in 2011 to conduct additional trials. This includes the development of clinical trials for the treatment of NF complications, including plexiform neurofibromas, cognitive disorders, low-grade gliomas, vestibular schwannomas, and malignant peripheral nerve sheath tumors. Composed of 19 clinical sites, the NFCTC is led by the operations center based at the University of Alabama at Birmingham under the direction of Dr. Bruce Korf. The University 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.

***NFCTC***
To date, the NFCTC has successfully initiated 8 clinical trials and supported 3 additional trials. The NFRP offered the Clinical Trial Consortium Award again in FY16.

## Ovarian Cancer Academy (OCA)

> ***OCA***
> The Ovarian Cancer Research Program (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.

In FY09, a Dean and seven Early-Career Investigator (ECI) Awards marked the realization of the Ovarian Cancer Research Program's vision of a unique, virtual OCA that supports the development of career ovarian cancer researchers. The OCA brings together a group of talented and highly committed ECIs with their mentors and Academy Leadership. 2015 saw the transition in the OCA Leadership from the first Academy Dean, Dr. Patricia Donohoe of the Massachusetts General Hospital, to the OCA's new leadership, with Dr. Nita Maihle of the Georgia Regents University and Dr. Douglas Levine of Memorial Sloan-Kettering Cancer Center serving as the new Dean and Assistant Dean, respectively. Two of the original FY09 ECI awardees graduated from the OCA, and four new FY14 ECI-mentor pairs were welcomed into the OCA. The new Dean, Assistant Dean, and the ECIs participated in a pre-award meeting to facilitate the transition and set expectations for the OCA. The maturing ECIs have demonstrated remarkable progress, including over 170 publications and over 130 abstracts to date focused on ovarian cancer. Their growth as independent, committed ovarian cancer researchers is evident in the 62 funded grants obtained (including NIH R01s), as well as their service on the boards of well-established journals and women's cancer foundations. Additionally, since the inception of the OCA, the maturing ECIs have advanced well along the tenure track, mentored increasing numbers of personnel, and collaborated within the Academy on publications, grant applications, and technical ventures. The annual OCA in-person workshop in Chicago in March 2015 promoted further collaborations and fostered cross-mentoring within the group of ECIs. It preceded a special session at the annual Society of Gynecologic Oncology meeting, wherein the original seven FY09 OCA ECIs were invited speakers at the Special Interest Session VIII, entitled the "Department of Defense Ovarian Cancer Academy Abstract Session." To further expand and enrich the OCA, the OCA Collaborative Award mechanism was successfully introduced. The OCA Collaborative Award mechanism required applications from existing ECIs to include a partnering PI from outside the Academy on proposed research projects that were an offshoot or an idea that developed from research performed under the OCA ECI Awards.

## 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 majority of cases (61%) are diagnosed at late stages, for which the 5-year survival rate is 27% (United States, 2014). A multi-institutional team headed by Dr. Robert Kurman's research group at Johns Hopkins University, along with collaborators at the gynecologic oncology powerhouses of Memorial Sloan Kettering Cancer Center, the University of Toronto, and Yale University, successfully competed for the first Ovarian Cancer Consortium Award (OCCA) offered in 2010. 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 is testing 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.

***Ovarian Cancer Consortium***
This data will ultimately help to shape prevention and early detection approaches for ovarian cancer.

Major accomplishments of the consortium include:

- Evaluating STICS as precursor lesions of HGSCs: Via fluorescent in-situ hybridization studies, they demonstrated that CCNE1 (Cyclin gene) copy number gain occurs in 22% of STICs that are associated with HGSCs, suggesting that amplification of CCNE1 is a mechanism in STIC development. They also found that centrosome amplification in tumor cells was more frequently detected in HGSCs than STICs, indicating a progressive acquisition of chromosomal instability during tumor progression. Furthermore, they identified five ovarian cancer-associated markers on STICs via immunohistochemistry: LAMC1 (Laminins), CCNE1 (Cyclin), topoisomerase II, RSF-1 (Remodeling and Spacing Factor 1), and the loss of ALDH1A1 (Aldehyde Dehydrogenase 1 Family, Member A1). Additionally, their early findings show that the important cancer gene TET1 (Tet Methylcytosine Dioxygenase) is upregulated at the early STIC stage, in addition to HGSCs.
- Assessing all of the sites proposed as the origin of HGSCs: Analysis of 228 cases found that STIC lesions are present in ~ 41% of cases with HGSC of pelvic origin. The data and results indicate that nearly all HGSCs develop from the distal fallopian tube through STICs, since little genomic variation has been found between HGSCs tumors with and without STICs.
- Identifying the early molecular changes that precede the development of STICs: Microarray data comparison of malignant HGSCs and non-malignant ovarian tissue samples suggests that increased tumor risk in the fimbria is likely due to differences in hormonal expression between fimbria and ampulla.

## Ovarian Cancer Outcomes Consortia

In FY12, the 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 ovarian cancer patients. The intention was to bring together teams of talented researchers to focus on discovering what distinguishes the small subset of ovarian cancer patients who become long-term survivors (≥ 10-year survival from diagnosis) from other ovarian cancer survivors. In FY15, the OCRP offered the Outcomes Consortium Award to move the consortiums from the

development phase to the research phase, where each consortium 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.

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, will be studying the role of the patients' immune response; their genetics, especially those related to DNA repair; and epidemiological and lifestyle factors that contribute to long-term survival. The MOCOG is a 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 Long-Term Survival, led by Dr. Birrer at Massachusetts General Hospital, will focus on finding predictive biomarkers that will help in the design of individualized care for ovarian cancer patients.

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

## Pharmacotherapies for Alcohol and Substance Abuse Consortium

On September 30, 2015, Research Triangle Institute (RTI) was awarded a $10.8M 5-year award from the FY14 Alcohol and Substance Abuse Disorders Research Program Consortia Award Program Announcement. The Consortium is led by Dr. Rick Williams from RTI, in collaboration with Baylor College of Medicine and the Uniform Services University of Health Sciences. The Pharmacotherapies for Alcohol and Substance Abuse Consortium has three aims in developing pharmacotherapies for alcohol and substance abuse disorders (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. Eight project awards are planned for FY16.

## Prostate Cancer Clinical Trials Consortium (PCCTC)

The PCCTC has received support from the Prostate Cancer Research Program (PCRP) since 2005 and, in February 2014, became a limited liability company (Prostate Cancer Clinical Trials Consortium, LLC). Led by Memorial Sloan Kettering Cancer Center, the PCCTC currently has 11 sites funded with PCRP grants and over 20 participating affiliated sites supported with other funding. The PCCTC also has contracts with four pharmaceutical companies and is in the negotiation process with three additional companies to develop contracts to collaboratively run clinical trials for new developing therapies for prostate cancer. The PCCTC has 182 clinical trials approved for activation, of which 129 have been completed (closed to accrual), with an additional 49 trials either active or pending activation. Over 5,299 patients have been enrolled in these trials, 10%

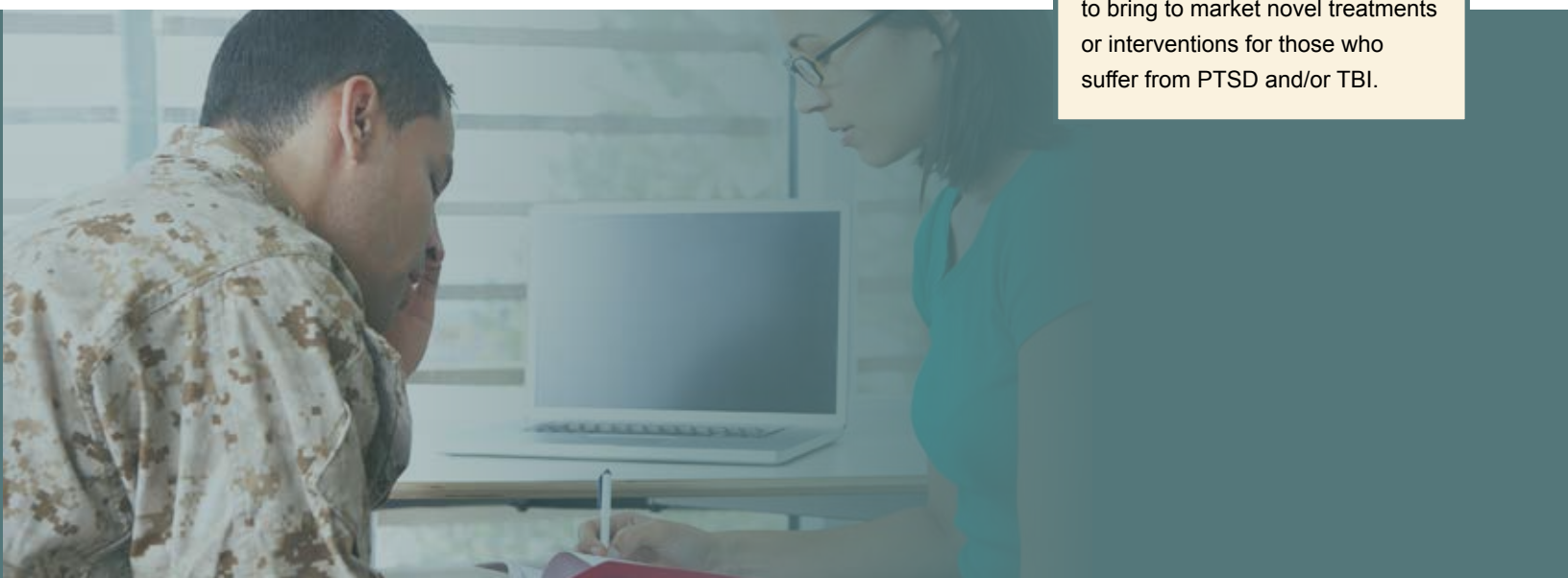
***PCCTC***
The PCCTC has established itself as the nation's premier prostate cancer clinical trials group and remains poised to make a significant impact on the lives of patients by keeping the drug pipeline primed with promising novel agents.

representing patients from disproportionately affected populations. Since biomarkers are increasingly being recognized as essential in the evaluation of treatment response, as well as for risk assessment, early detection, prediction of aggressiveness, and/or progression of prostate cancer, biomarker studies are being strongly pursued and validated across institutions. In 2008, PCCTC investigators led a collaborative initiative, the Prostate Cancer Working Group, to issue recommendations on the design and endpoints for prostate cancer clinical trials. These recommendations have had a profound impact on the clinical research community and how clinical trials are designed, and Consortium investigators recently published an update to this effort in the *Journal of Clinical Oncology*. The PCCTC's extensive clinical trial experience and collaborative efforts have helped bring numerous potential new therapeutics into Phase III clinical trials, with two agents having now received approval by the FDA: (1) abiraterone acetate, which blocks formation of testosterone by inhibiting CYP17A1, and (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. 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.

## PTSD and TBI Clinical Consortium Award – INTRuST

The INjury and TRaumatic STress (INTRuST) Consortium is comprised of the coordinating center, located at the University of California, San Diego; 10 competitively selected clinical sites; a Biorepository Core; a Neuroimaging Repository Core; a Biostatistics Core; an Informatics Core; and 19 additional military treatment and Veterans' facilities—all conducting clinical trials or collecting samples for clinical trials in PTSD and/or TBI. In its final year, the INTRuST Consortium has completed three randomized, controlled clinical trials; a prospective cohort study; and seven pilot studies. The portfolio of clinical trial advances spans psychotherapies to drug therapies to device therapy (e.g., transcranial magnetic stimulation of the prefrontal cortex). All trials are designed to decrease the impact of military-relevant PTSD and TBI for the benefit of Service Members, their families, their caregivers, and the American public. Additional information about the individual studies can be found at http://intrust.sdsc.edu/clinicalTrials.html. In addition, the repositories will serve as a resource for future investigators, providing blood and DNA/ribonucleic acid samples, as well as neuroimages of clinical trial subjects. These data can be shared with other collaborative research groups upon request. A public data set with accurate TBI and PTSD phenotypes is available as well. This consortium mechanism has provided clinicians with a new understanding of the PTSD–TBI interface and has established valuable infrastructure and scientific collaborations that will continue into the future.

***INTRuST***
The INTRuST Consortium was established to combine the research efforts of the nation's leading experts on PTSD and TBI to bring to market novel treatments or interventions for those who suffer from PTSD and/or TBI.



## PTSD Multidisciplinary Research Consortium Award – STRONG STAR

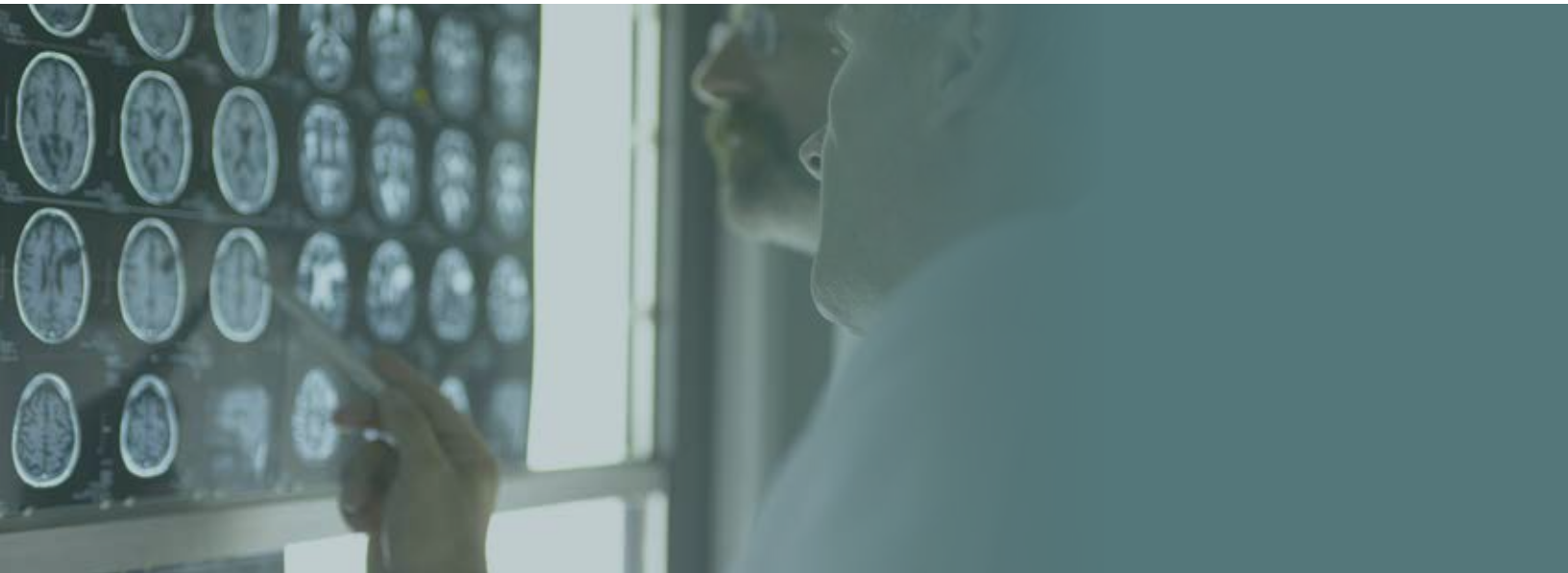
The South Texas Research Organizational Network Guiding Studies on Trauma and Resilience (STRONG STAR) is dedicated to the development and evaluation of the most effective interventions for the detection, prevention, and treatment for combat-related PTSD. The STRONG STAR team of approximately 100 military, 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 15 collaborating investigators from across the country. The STRONG STAR Consortium is conducting 11 projects, including retrospective data analyses, epidemiological studies, a data repository, a biorepository, and 8 clinical studies. The results of one animal study and one neuroimaging study 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 expected to be available in 2016–2017.

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

## TBI Multidisciplinary Research Consortium Award – Mission Connect

Mission Connect was established in 1997 by the Institute for Rehabilitation and Research Foundation to address difficult problems in neurotrauma research by capitalizing on the expertise and research at the Texas Medical Center in Houston, Texas. Under the FY07 Psychological Health and Traumatic Brain Injury Research Program (PH/TBIRP), Mission Connect was funded to improve the diagnosis and treatment of mTBI through collaborative basic and clinical research. With its final year completed, Mission Connect has made several contributions to the field. In a longitudinal study that follows mTBI patients from the first 48 hours to 6 months post injury, researchers have used advanced MRI protocols to uncover a correlation between loss of consciousness and neuronal tract disruption in patients within the first 48 hours of mTBI and 3 months post injury. Researchers have developed a functional MRI biofeedback protocol that improves the function of damaged neural networks of mTBI patients. Investigators also performed preclinical evaluations of several promising treatments in animal models characterized and standardized within the Consortium. One of the most promising agents, ARA290, is being further developed using funding from the NIH and an industry partner. Researchers have recently completed the final analysis of a Phase II Clinical Trial using the FDA-approved drug Atorvastatin (Lipitor®) as a potential treatment for mTBI. While Atorvastatin treatment did show a trend for improvement in primary outcome measure, the Rivermead Post-Concussion Symptoms Questionnaire, the findings were not statistically significant. This may be partially due to the enrollment target not being met. Clinical data from Mission Connect is also being utilized in the Stage I effort of the Traumatic Brain Injury Endpoints Development Award (read more about this award on the next page).

***Mission Connect***
Mission Connect was funded to improve the diagnosis and treatment of mTBI through collaborative basic and clinical research.



## Team Approach to the Prevention and Treatment of Post-Traumatic Epilepsy (TAPTE)

***TAPTE***

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

The ultimate goal will be to use this research to prevent the development of post-traumatic epilepsy (PTE) from TBI. Based on previous successes within the epilepsy community, the Citizens United for Research in Epilepsy (CURE) Foundation will use their scientific model to rapidly advance the most promising research in PTE. The model will build a "critical mass" of investigators with similar research interests and diverse backgrounds to address and execute PTE research via a team science approach. The investigative team will work closely with the CURE Foundation, who will proactively monitor research progress and advise the Consortium on which directions to take to ensure ultimate success. Key opinion leaders in both TBI and epilepsy research have been assembled to guide the development of a Request for Applications and their subsequent review. The opinion leaders will work closely with the Consortium to ensure the TAPTE's goal will be reached, and the two groups will have continuous dialog mediated by the CURE Foundation.

## Traumatic Brain Injury Endpoints Development (TED) Award

***TED***

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

With FY13 PH/TBIRP funding, the TED Award mechanism 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, 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 is focused on integrating existing data and identifying the most promising endpoints to move forward, with contributions from expert working groups, consensus decisions, and close interactions with the FDA. Stage II allows for larger-scale validation studies of candidate clinical outcome assessments and biomarkers selected in Stage I, leveraging existing research infrastructure and clinical study networks of Transforming Research and Clinical Knowledge in Traumatic Brain Injury, the Concussion Research Consortium, and the CENC.

## Understanding Gulf War Illness: An Integrative Modeling Approach

Under the leadership of Dr. Mariana Morris, Dr. Nancy Klimas, and Dr. Gordon Broderick, this GWIRP-funded Consortium represents expertise in neurotoxicology, animal modeling, computational modeling, clinical research, and drug development. This multidisciplinary research team, based at the Institute for Neuroimmune Medicine at Nova Southeastern University,

aims to develop a translational model of GWI that will rapidly 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; and observational studies of symptomatic Gulf War Veterans, efforts are integrated to discern the pathways and mediators underlying GWI. The key mediators identified from the model will then be targeted with potential therapeutic interventions that will address the altered homeostasis of GWI. Finally, the two or three best-performing pharmacological treatments will be tested in a well-defined Gulf War Veteran cohort.

## Networking with Federal and Non-Federal Agencies

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. 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 provides a check and balance for duplicative research efforts, as well as an opportunity to encourage complementary investment strategies. Examples of interagency collaborations include, but are not limited to, the following:

***Advisory Committee on Breast Cancer in Young Women***

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

***Federal Interagency Traumatic Brain Injury Research 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 disorders (ASDs). Federal and non-federal members are included on the committee to ensure that a wide range of ideas and perspectives pertaining to ASDs is represented and discussed in a public forum.

***Interagency Urology Coordinating Committee***

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

***Networking with Federal and Non-Federal Agencies***

These interagency collaborations strive toward synergy with other agencies and diversification of funded research portfolios, underscoring the importance of research coordination efforts.

***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.

***Metastasis Cancer Research Task Force***

As directed by Congress to the Assistant Secretary of Defense (Health Affairs), an interagency group led by the Murtha Cancer Center that is tasked to provide recommendations on research for metastasized cancer, with a focus on extending the lives of advanced-state and recurrent patients.

***Muscular Dystrophy Coordinating Committee***

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

***National Alzheimer's Project Act***

A group that combines federal efforts to coordinate Alzheimer's Disease and Related Dementia (ADRD) research. The National Plan for 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.

## Small Business Innovation Research (SBIR) & Small Business Technology Transfer (STTR) Programs

***USAMRMC SBIR and STTR Program Objectives:***

- Stimulate technological innovation
- Increase private-sector commercialization of federal research and development
- Increase small business participation in federally funded research and development
- Foster participation by minority and disadvantaged firms in technological innovation

Established by Congress, the goal of these programs is to provide small businesses with critical startup and development support that will allow them to compete successfully with larger businesses and commercialize products while fulfilling government needs. Eleven federal agencies participate in the SBIR program, and five participate in the STTR program, including the DoD. The CDMRP has worked with these programs since FY00 and FY04, respectively, to fill gaps and leverage research and product development not supported elsewhere in the CDMRP portfolio. Since that time, the CDMRP managed more than $70M in SBIR and STTR awards from the overall USAMRMC SBIR and STTR programs.

***SBIR and STTR***

The SBIR and STTR programs are competitive funding opportunities designed to strengthen the role of innovative small businesses in federally funded research and development.

For more information about these programs, please see pages 96–97.

# Our Programs

The 28 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

## Program History

The problem of alcohol and substance abuse is a growing concern among the general public, as well as military personnel and Veterans alike. In 2013, the Institute of Medicine (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%. Rates of acute and chronic incident alcohol diagnoses increased from 2001 through 2010, especially for the active duty component. The results indicate the increasing medical burden imposed on the Military Health System by excessive alcohol use. Substance abuse was involved in 30% of the Army's suicide deaths from 2005–2009 (National Institute of Drug Abuse 2011). Furthermore, alcohol and substance use disorders (ASUD) significantly worsen the hyper-arousal effects of PTSD, a disorder that affects 14% of all previously deployed U.S. military personnel (RAND 2012). Veterans have their PTSD complicated by chronic TBI effects, which are worsened by ASUD. The 2013 IOM report recommended that the DoD assume leadership to ensure the consistency and quality of treatment services available to those with ASUD, given the burden of ASUD in the military. The Alcohol and Substance Abuse Disorders Research Program (ASADRP) was established in FY10 with a congressional appropriation of $6.375M. Since then, the program has established a network of multidisciplinary, translational research teams with the explicit goal of accelerating the delivery of new or improved treatments for ASUD, and federal funding for its research has led to a total appropriation of $32.075M to the ASADRP. The goal of the program is to identify and develop new medications to improve treatment outcomes for substance use disorders (SUDs), especially those related to TBI and PTSD. The program's approach is to organize multidisciplinary, team-based, translational research efforts to identify promising compounds, conduct proof-of-principle basic research to determine which compounds are most appropriate for human research trials, and conduct human proof-of-principle trials with promising compounds. If successful, this approach could result in translation of contemporary basic science knowledge into enhanced clinical pharmacological treatment protocols for ASUD.

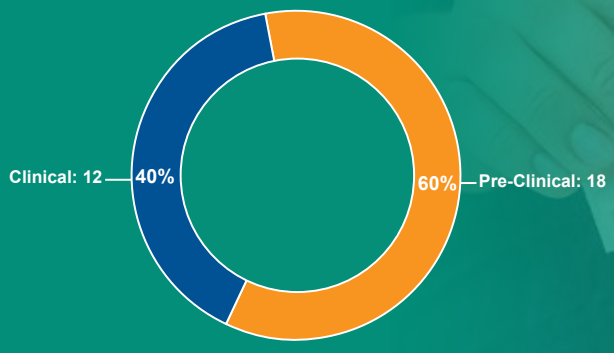
## Vision

Decrease the clinical impact of alcohol and substance abuse

## Mission

Explore new opportunities to address alcohol and substance abuse disorders, especially related to TBI and PTSD, through multidisciplinary, team-based research efforts that translate basic knowledge into enhanced clinical protocols

### FY10–FY14 Portfolio by Research Area




**Total number of awarded projects: 30**
**Total number of active projects: 18**

## Glial Regulators for Treating Comorbid Posttraumatic Stress Disorder and Substance Use Disorders

**Sudie E. Back, Ph.D., Medical University of South Carolina**

Data from the proof-of-principle study among 35 Veterans with PTSD and SUD (primarily alcohol use disorder [AUD]) showed that NAC treatment was associated with an 81% reduction in craving, which was significantly greater than the placebo group (32%). Scores on the Clinician Administered PTSD Scale (CAPS) and the Beck Depression Inventory (BDI) were also significantly reduced in the NAC, but not in the placebo group. These robust results led to a recently initiated full-scale, 8-week, randomized, controlled trial of NAC (2,400 mg) vs. placebo among Veterans (N=90) with PTSD and AUD. In addition, the new study is utilizing functional magnetic resonance imaging and proton magnetic resonance spectroscopy before and after treatment.

## Epigenetic Modulation of Interactions between Fear and Substance Abuse

**Kennon M. Lattal, Ph.D., Oregon Health & Science University**

SUD and PTSD are highly comorbid, with PTSD symptoms causing relapse in drug seeking, even after successful treatment and long periods of abstinence. This project aims to develop a novel rodent model for the comorbidity between SUD and PTSD, and to use this model to test a novel pharmacological intervention that, when paired with behavioral interventions, reverses drug-seeking and anxiety induced by specific memories. The investigators have successfully established a novel procedure for studying the interactions between fear-conditioning and drug-seeking and have established HDAC3 inhibitors as a potential therapeutic for promoting extinction of fear and drug-seeking behaviors. Importantly, they have demonstrated that the fear-conditioning procedure that they previously found to have lasting effects on methamphetamine-seeking also has an effect on alcohol-seeking behavior and may provide data relevant to multiple types of drug abuse.

## Development of an Animal Model and Novel Treatments for Comorbid PTSD and Cocaine Addiction

**Lori A. Knackstedt, Ph.D., University of Florida**

The objective of this project is to develop a novel animal model of comorbid PTSD and cocaine use disorder and examine medications that target the glutamate and endocannabinoid systems for their ability to reduce both PTSD symptoms and cocaine-seeking. The investigators have successfully shown that stress-susceptible (PTSD-like) rats displayed enhanced cocaine-seeking compared to resilient and unstressed control rats. The antibiotic ceftriaxone effectively prevented cocaine-seeking only in the resilient and unstressed control rats, indicating that medications that treat cocaine addiction in non-PTSD individuals may be unable to do so in PTSD patients. However, the combination of ceftriaxone with CDPPB, which also targets the glutamate neurotransmitter system, completely prevented cocaine-seeking in PTSD rats. Future studies will examine additional experimental compounds in an effort to guide successful treatment of comorbid PTSD and cocaine use in those suffering from these disorders.

## The Pharmacotherapies for Alcohol and Substance Abuse (PASA) Consortium

**Rick Williams, Ph.D., Research Triangle Institute International (RTI)**

**The PASA is a multicenter collaboration led by Dr. Rick Williams of RTI and its partners, Baylor College of Medicine and the Uniformed Services University of Health Sciences. PASA uses a translational approach (from animal models to humans) to understand the complex interaction of substance abuse with the now-common military stress comorbidity of associated PTSD and TBI. New pharmacotherapies for treatment of ASUD and combined disorders are needed to improve health outcomes and adherence to treatment, as well as reduce costs to the military. PASA has recently funded four studies, (two pre-clinical and two clinical):**

- **Assessing pharmacotherapies in animal models of PTSD and AUD**
- **Preclinical Analysis of Combined Carisbamate and Doxazosin Treatments in Stress-Alcohol Drinking Models**
- **Carisbamate as a New Treatment for PTSD and Co-Occurring AUD**
- **Efficacy and Safety Study of ORG 34517 in Veterans with Comorbid PTSD/AUD**

# Amyotrophic Lateral Sclerosis Research Program

## Program History

Amyotrophic Lateral Sclerosis (ALS), also known as "Lou Gehrig's disease," is an incurable, degenerative neurological disorder without a cure. The CDMRP 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 with a $5M appropriation. Although the ALSRP was not funded in FY08, Congress subsequently appropriated funding in FY09 and has continuously provided funding since then with a total appropriation of more than $61M, including $7.5M in FY16. 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 define targets with therapeutic potential and development of pharmacologic agents through the adsorption, distribution, metabolism, excretion, and toxicity (ADMET) stage or Investigational New Drug (IND) application submission.

For FY16, the Programmatic Panel faces the challenge of continuing this effort of promoting innovative preclinical research toward novel ALS therapeutics.

The pie chart shows the number of awards the program has supported from FY07 through FY15.

## Vision

Improve treatment and find a cure for ALS

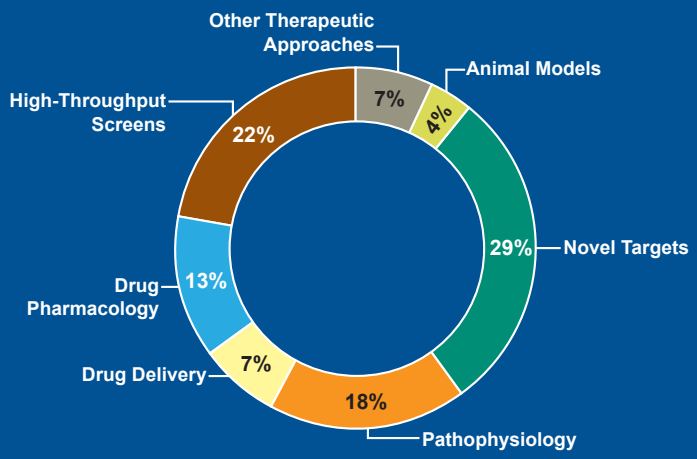
## Mission

Fund Innovative pre-clinical research to develop new treatments for ALS

**Larry Mink, Ph.D., FY15–FY16 ALSRP Programmatic Panel Member**

**"**It has been my privilege to be part of the ALSRP Programmatic Panel as a consumer reviewer. The quality of research projects that ALSRP funds gives me hope that effective treatments for this horrific disease will be found in the not too distant future.**"**

### 2007–2015 ALSRP Funding Categories



## Developing ER Stress Inhibitors for Treating ALS

**Nicholas Cosford, Ph.D., Sanford Burnham Prebys Medical Discovery Institute**

While the exact cause of ALS is unknown, a prominent pathological feature of the disease implicates upregulation of endoplasmic reticulum (ER) stress signaling in the motor neurons of affected individuals. Apoptosis signal-regulating kinase 1 (ASK1) is an important signaling molecule involved in the ER stress response, and its activation has been associated with motor neuron death in ALS models. Dr. Nicholas Cosford of the Sanford Burnham Prebys Medical Discovery Institute used an ALSRP Therapeutic Development Award to design and evaluate benzodiazepinone analogue compounds as small molecule modulators of the ASK1 pathway. In addition to mechanism of action studies, various benzodiazepinone compounds were tested for microsomal stability, plasma stability, and parallel artificial membrane permeability (an indicator of blood-brain barrier permeability). These pharmacokinetic assays have supported further in vivo evaluation of several candidates. Further characterization in zebrafish and mouse ALS models is ongoing, as these benzodiazepinone compounds hold promise as potent ER stress inhibitors for continued clinical development.

## Development of Copper ATSM as a Therapeutic for SOD-Familial and Sporadic ALS

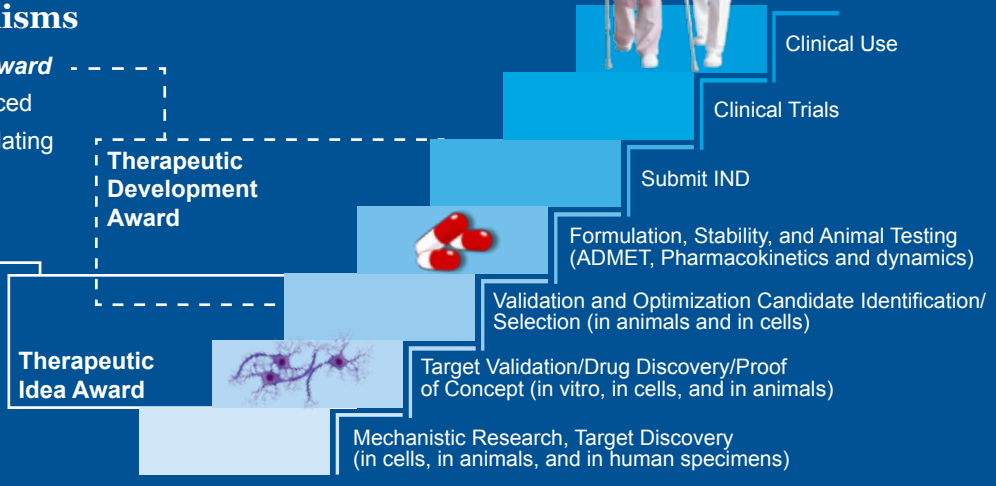
**Joseph Beckman, Ph.D., Oregon State University**

Dr. Joe Beckman and his team at Oregon State University are investigating the role of copper in the pathophysiology of ALS. This group proposes that the intracellular copper complex CuATSM might be able to selectively provide copper to mutant super oxide dismutase (SOD) neurons in the spinal cord. CuATSM is already used as an imaging agent to identify certain tumors in humans, has low toxicity, and has been shown to penetrate the blood-brain barrier of ALS patients. Beginning with a structural lead of CuATSM, shown to reduce toxicity while increasing maturation of SOD in vivo, Dr. Beckman is further optimizing structure and delivery in a mouse model under an FY14 ALSRP Therapeutic Development Award. He expects completion of this project will result in a CuATSM derivative that maximizes survival and the successful development of essential data needed by the FDA for Phase I trials to determine safety and dosage. Dr. Beckman proposes that CuATSM could be a treatment for both SOD-familial and sporadic ALS patients.

## ALSRP Award Mechanisms

The ***Therapeutic Development Award*** is intended to support more advanced preclinical research aimed at translating therapeutic compounds and other treatments closer to clinical trials.

The ***Therapeutic Idea Award*** supports new ideas aimed at early stage drug/target discovery.



# Autism Research Program

## Program History

Since its inception in FY07 through FY16, appropriations totaling $66.9M have been directed to the Autism Research Program (ARP) to promote innovative research that advances the understanding of autism spectrum disorders (ASD). The immediacy of the ARP 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 the 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, such as anxiety, gastrointestinal 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. The ARP focuses on funding innovative and highly impactful research while trying to complement other funding agencies initiatives. Recent progress by investigators funded by the 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) enhancing research tools to assist scientists on their quest to understand and improve the lives of individuals living with autism.

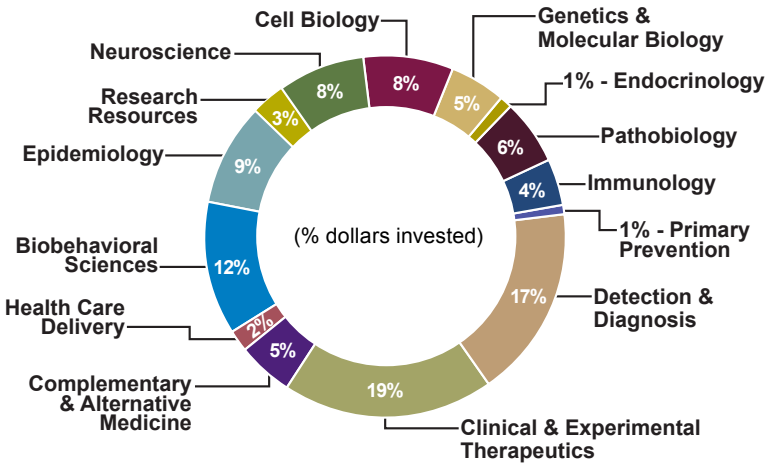
## Vision

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

## FY07–FY15 Research Portfolio




**Ms. Shelley Hendrix**

**"I am so honored to serve on the Integration Panel of the CDMRP Autism Research Program, which embraces consumers as an integral part of the process in selecting research that is most relevant to our community. Our input is valued in equal measure to our scientific and clinical community counterparts. Allowing this type of cross-pollination gives our community a voice to explain what life beyond the laboratory and treatment rooms is like for families living with autism. That improved understanding helps all of us focus on our ultimate mission and vision of improving the lives of those with autism spectrum disorders now, in real time, to improve their ability to grow up and live independent, meaningful, and fulfilling lives."**

**Dwight German, Ph.D., and his team at the University of Texas Southwestern Medical Center** used screening of a combinatorial peptoid library to search for blood biomarkers for ASD. He found one peptoid, ASD1, which bound ~50% less serum IgG1 in ASD boys compared with typically developing boys. The binding level of the ASD1 peptoid negatively correlated with communication scores measured in the Autism Diagnostic Interview-Revised Test, which quantifies characteristics of reciprocal social interaction, communication, language, and repetitive behaviors. The ASD1 peptoid did not have sufficient predictive accuracy (66%) to stand alone as a biomarker for ASD. However, Dr. German was able to use additional protein library screening to identify 11 serum proteins that differed significantly between ASD and typically developing boys, including thyroid-stimulating hormone (TSH), IL8, monokine induced by gamma interferon, and apolipoprotein E, among others. When combined with analysis of serum TSH levels, the predictive accuracy of ASD1 rose to 73%. The identification of these and additional biomarkers may be useful in the development of an assay that could identify and subsequently allow access to treatment for ASD earlier in life.

**Georgianna Gould, Ph.D., and her team at the University of Texas Health Science Center at San Antonio** sought to identify new therapeutic targets for the treatment of impaired social behavior in ASD patients. Dysfunction of the brain's serotonin (5-HT) neurotransmitter system, which regulates diverse behavioral and autonomic processes, may contribute to social interaction deficiencies in ASD. Some behavior-modifying drugs, including Prozac, improve sociability by blocking the major serotonin transporter (SERT) that shuttles 5-HT from the extracellular spaces in the brain into neurons. However, these drugs are efficacious in only a subset of autism patients, possibly because other auxiliary 5-HT transporters, including organic cation transporter 3 and plasma membrane monoamine transporters, may compensate for blockage or dysfunction of SERT. Dr. Gould's team tested a drug that blocks these transporters, pseudoisocyanine decinium-22 (D-22), to determine whether this may be an effective treatment for ASD. With the use of inbred ASD mouse models, they found that sociability indices such as social sniffing and dwelling near unfamiliar mice increased in D-22-treated mice that would otherwise display deficiencies in social interaction. These results suggest that targeting auxiliary 5-HT transporters may be a promising therapeutic avenue for the treatment of social behavioral deficiencies in ASD individuals.

**Dr. Cade Nylund and his team at the Uniformed Services University of the Health Sciences examined Department of Defense Military Health System medical records to understand comorbid conditions and risk factors for autism. The researchers studied records from 48,762 children with ASD, ages 2–18, and 243,810 children without ASD (age- and gender-matched). They found that children with ASD were more than twice as likely as matched controls to be obese. ASD children were also at risk for nutritional deficiencies in several macro- and micro-nutrients, including iron, vitamin A, calcium, vitamin D, and protein. Additionally, Dr. Nylund's team identified multiple prenatal and early infancy ASD risk factors, including birth asphyxia, preterm birth, low birth weight, newborn infections, newborn epilepsy/seizure, and newborn complications. Maternal medical conditions associated with eventual diagnosis of ASD in their children included high blood pressure, asthma, mental health problems, hyperemesis, and obesity. Women who had fertility treatments, received medication during pregnancy, or had pregnancy or labor complications also had increased risk for the development of ASD in their children.**

# Bone Marrow Failure Research Program

## Program History

The marrow of bones is made up of a spongy tissue containing the bio-manufacturing mechanism of blood cells where stem cells initiate the hematopoietic cascade for the development of all of the different cells within the blood, including red blood cells, white blood cells, and platelets. Disorders affecting the stem cells or progenitor cells can lead to bone marrow failure–rare, potentially life-threatening diseases in which the bone marrow stops functioning or produces abnormal blood cells. These diseases are classified into two major categories: inherited bone marrow failure and acquired bone marrow failure. Inherited bone marrow failure is a group of diseases where somatic genetic mutations lead to a deficiency in hematopoiesis that presents in childhood or early adulthood. Acquired bone marrow failure is a group of diseases that can occur following an environmental exposure such as ionizing radiation, chemical contamination, or long-term effects of chemotherapeutics to cure other diseases. Both types of bone marrow failure lead to life-long chronic illnesses with the potential to develop cancer. In FY08, the U.S. Congress appropriated $1M for bone marrow failure research. With continued appropriations, the Bone Marrow Failure Research Program (BMFRP) was established. From FY08 through FY15, $26.2M has been appropriated by Congress to research the prevention, causes, and treatment of bone marrow failure diseases. The appropriation for FY16 for the BMFRP is $3M. Thus far, the BMFRP has invested in 56 awards, with the mission to support innovative research committed to advancing the understanding of inherited and acquired bone marrow failure diseases.

## Vision

To understand and cure bone marrow failure syndromes

## Mission

To encourage and support innovative research that is committed to advancing the understanding of inherited and acquired bone marrow failure syndromes, thereby improving the health of affected individuals, with the ultimate goals of prevention and cure

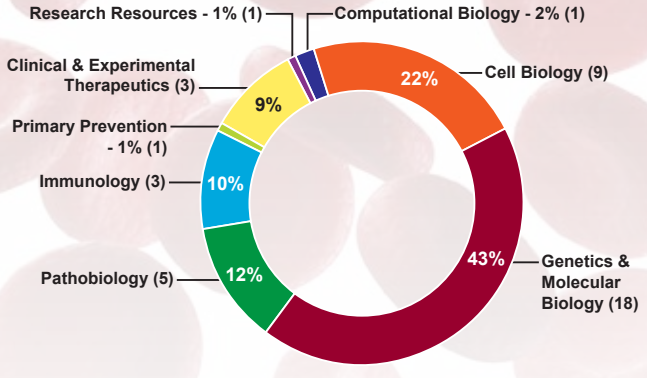
## Examples of *inherited* bone marrow failure:

- Fanconi anemia
- Dyskeratosis congenital
- Shwachman-Diamond syndrome
- Diamond-Blackfan anemia
- Neutropenia

## Examples of *acquired* bone marrow failure:

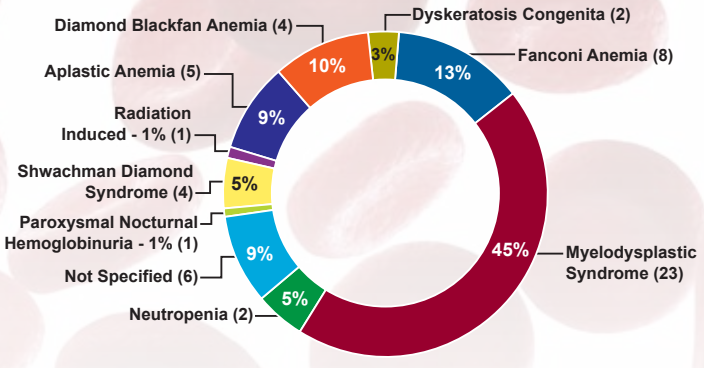
- Aplastic anemia
- Myelodysplasia
- Paroxysmal nocturnal hemoglobinuria
- Pure red cell aplasia

### FY08–FY15 Research Portfolio Percent Dollars Invested*




*Percentages of total spent and (number of awards)

### FY08–FY15 Disease Classification*



## Understanding and Targeting Epigenetic Alterations in Acquired Bone Marrow Failure

**Omar Abdel-Wahab, M.D., Memorial Sloan Kettering Cancer Center**

The myelodysplastic syndromes (MDS) are disorders of the hematopoietic cascade within the bone marrow, leading to anemia and cytopenias, with potential progression to leukemia. With support from a BMFRP FY12 Postdoctoral Fellowship Award, Dr. Omar Abdel-Wahab has made significant discoveries in how various gene mutations contribute to the development of bone marrow failure in MDS patients. Dr. Abdel-Wahab's group discovered that a class of mutations frequently found in MDS patients affecting the ribonucleic acid (RNA) splicing machinery can impact the function of proteins involved in maintaining the epigenome. This finding implicates the critical role that the RNA splicing machinery plays in hematopoiesis and bone marrow failure. Furthermore, he has shown that mutations in genes responsible for chromatin remodel and gene-silencing results in the decreased function of a protein complex involved in stem cell differentiation and early embryonic development. Dr. Abdel-Wahab's work has resulted in the development of the first conditional knockout mouse for Asxl1, as well as the first mouse model with combined Asxl1 and Tet2 deletion. These mice may serve as necessary resources to understanding the biology of MDS and developing new therapies.

## Shwachman Diamond Syndrome Linking Bone Marrow Failure to Global Acetylome Dysregulation

**Paul de Figueiredo, Ph.D., Texas A&M Research Foundation**

Shwachman Diamond syndrome (SDS) is an inherited bone marrow failure syndrome whose hallmark is a combination of neutropenia and exocrine pancreatic dysfunction, with some patients progressing to malignant myeloid transformation and leukemia. SDS involves critical mechanisms underlying both hematopoiesis and leukemogenesis. The gene, SBDS, is mutated in nearly all cases of SDS. With support from an FY10 BMFRP award, Dr. Paul de Figueiredo's group performed a screen to find a compound that would reverse the SDS phenotype in yeast cells. Trichostatin A (TSA), a histone deacetylase (HDAC) inhibitor currently used as an anti-inflammatory agent, was a small molecule that showed the most promising results. HDAC inhibitors induce expression changes of genes that may involve cell growth. Dr. de Figueiredo's research team found that TSA and suberoylanilide hydroxamic acid (an FDA-approved HDAC inhibitor) promoted the growth of both yeast and human cells, thus demonstrating that these inhibitors may correct the resulting SDS phenotype. These results suggest that the repurposing of FDA-approved HDAC inhibitors may be an appealing strategy for addressing the hematological dysfunctions associated with SDS.

## Functional Role of microRNAs in Hematopoietic Stem Cells in the Myelodysplastic Syndromes

**Christopher Park, M.D., Ph.D., Memorial Sloan Kettering Cancer Center**

With support from an FY10 New Investigator Award, Dr. Christopher Park's team compared MDS patient-derived bone marrow hematopoietic stem cells (HSCs) with age-matched controls and found 31 differentially expressed miRNAs. They focused on two particular miRNAs – miR-125 and miR-99 – and showed that decreased levels of miR-125b induced morphologic dysplasia and decreased colony formation of mouse progenitor cells. Overexpression of miR-125b enhanced HSC self-renewal, promoted a lymphoid bias, and reversed most of the age-related changes, including the promotion of increased numbers of committed hematopoietic progenitors and mature lymphoid cell production. Additionally, decreased expression of miR-99 in mouse HSCs reduced their self-renewal capacity and induced differentiation to the myeloid lineage. Dr. Park's group showed miR-125b expression in aged HSCs could be restored by anti-longevity regimens that also rejuvenate HSC function, such as calorie restriction and rapamycin treatment, suggesting avenues as possible treatment strategies for MDS.

# Breast Cancer Research Program

## 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 $3.2B in congressional appropriations through FY16. The BCRP seeks to make breakthroughs in breast cancer, accelerate high-impact research with clinical relevance, facilitate collaborations and partnerships, support future breast cancer leaders, and encourage innovation and creativity.

## Overarching Challenges

The BCRP recognizes that many overarching questions still remain unanswered in breast cancer, and that funding must be invested in critical areas of research in order to make breakthroughs that will save lives. To meet this urgent need, the FY16 BCRP requires applications to address at least one of the following overarching challenges:

- Prevent breast cancer (primary prevention)
- Identify determinants of breast cancer initiation, risk, or susceptibility
- Distinguish deadly from indolent breast cancers
- 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 (recurrence); determine how to prevent recurrence
- Revolutionize treatment regimens by replacing them with ones that are more effective and less toxic
- Eliminate the mortality associated with metastatic breast cancer

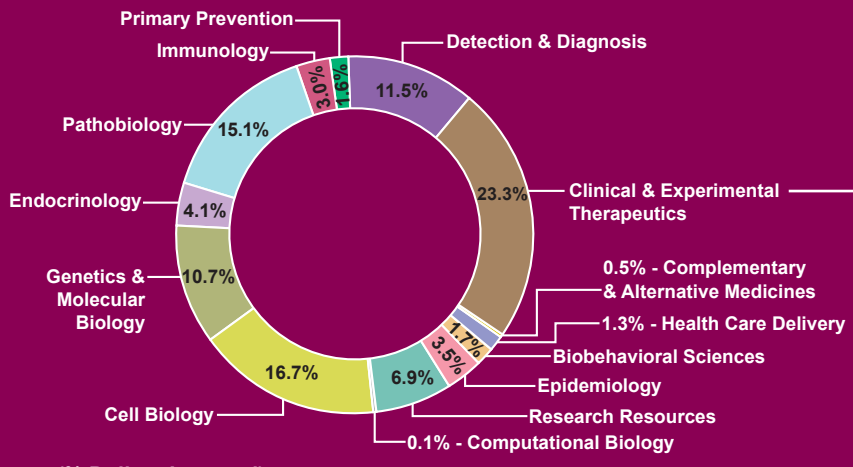
## Vision

To end breast cancer by funding innovative, high-impact research through a partnership of scientists and consumers

**E-8/SMSgt (Ret) Sheila Johnson-Glover**

**"**The DoD funded Dr. Dennis Slamon's early work on Herceptin® and thus benefited 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.**"**

## FY93–FY15 BCRP Research Portfolio




(% Dollars Invested)

## Immunotherapy Clinical Trials Enrolling in 2016

**Mary (Nora) Disis, University of Washington**

**Phase I clinical trial of the safety and immunogenicity of a multiple antigen vaccine (STEMVAC) in HER2-negative breast cancer. NCT02157051**

**William Gillanders, Washington University**

**Phase Ib clinical trial testing the safety and immune response to a Mammaglobin-A DNA vaccine in breast cancer patients undergoing neoadjuvant endocrine therapy. NCT02204098**

**Elizabeth Mittendorf, M.D. Anderson Cancer Center**

**Phase II clinical trial of combination immunotherapy of NeuVax™ and Herceptin® in high-risk HER2-positive breast cancer. NCT02297698**

## An Injectable Nanoparticle Generator Enhances Delivery of Cancer Therapeutics

**Mauro Ferrari, Ph.D., Houston Methodist Research Institute**

Numerous biological barriers prevent adequate drug delivery to tumors, thwarting effective tumor eradication. One method scientists are exploring to overcome these barriers is the use of nanoparticles, which are small particles that can be designed to target and deliver chemotherapeutic agents directly to tumor cells. Although promising in theory, nanoparticles have yet to be adopted into clinical practice. To improve the utility of nanoparticles, Dr. Mauro Ferrari, supported by an FY11 BCRP Innovator Expansion Award, created an injectable nanoparticle generator (iNPG) consisting of a nanopourous silicon particle loaded with the chemotherapeutic agent polymeric Doxorubicin (pDox). Using mouse models of breast cancer that has metastasized to the lung, Dr. Ferrari showed that iNPG-pDox selectively delivers pDox to tumor cells, while sparing surrounding tissues. Treatment resulted in a significant improvement in long-term survival and effectively cured almost half of the mice. Furthermore, cardiac toxicity was not seen following iNPG-pDox treatment, which is a common side effect that limits a patient's ability to tolerate treatment and eventually leads to cessation of therapy. In light of the promising results, Good Manufacturing Practices for this drug have been developed, and safety and efficacy studies in humans are planned to commence in 2017.

Xu R, et al. 2016. *Nature Biotechnology* 34(4):414-418.

## New Approaches to Eradicate Aggressive Breast Cancers

**Andrei Goga, M.D., Ph.D., University of California San Francisco**

It has recently been discovered that the oncogene MYC is elevated in triple-negative breast cancer (TNBC). With support from an FY11 Era of Hope Scholar Award, Dr. Andrei Goga has taken a multi-faceted approach to identifying new therapeutic targets in MYC-driven TNBCs. In the first part of the study, Dr. Goga's team isolated disseminated tumor cells (DTCs) from patient-derived xenograft models of breast cancer. Cells from high-burdened tissues expressed an elevated level of MYC. In addition, the DTCs from high-burdened tissues proved to be sensitive to the cyclin-dependent kinase inhibitor dinaciclib (Merck). After a four-week treatment course, DTCs were found in only 1 of 24 drug-treated mice, compared to 11 of 25 vehicle-treated mice. However, many animals still had significant primary tumors at the endpoint of the study, suggesting that the inhibitory effects of dinaciclib were greater on metastatic tumors than on primary tumors. Clinical trials of dinaciclib for the treatment of various cancers are already underway. In the second part of the study, using a metabolomics approach, Dr. Goga's team identified fatty acid oxidation (FAO) intermediates as being significantly upregulated in a MYC-driven model of TNBC. These results warrant further investigation into the inhibition of FAO as a therapeutic strategy for TNBC patients.

Lawson DA, et al. 2015. *Nature* 526(7571):131-135.

Camarda R, et al. 2016. *Nature Medicine* epub ahead of print (doi: 10.1038/nm.4055).

## Defining the Critical Role of Brain Metastases in Breast Cancer

**Dihua Yu, M.D., Ph.D., (pictured top) M.D. Anderson Cancer Center, University of Texas**
**Patricia S. Steeg, Ph.D., (pictured bottom) National Cancer Institute**

**An FY05 Breast Cancer Center of Excellence Award led by Dr. Patricia Steeg focused on solving the important problem of eradicating brain metastases in breast cancer. Dr. Dihua Yu contributed her expertise in the molecular biology of metastatic aggressiveness, as well as animal models. In November 2015, the team published a paper in *Nature* on how the loss of the tumor suppressor gene PTEN primes outgrowth of brain metastasis. Results showed that primary tumor cells lost normal PTEN expression after dissemination to the brain, but not to other organs, and regained it after leaving the brain. Exosomes from astrocytes were found to mediate intercellular transfer of miRNAs targeting PTEN expression in tumor cells. This adaptive PTEN loss increased secretion of the chemokine CCL2, which recruits myeloid cells that enhance outgrowth of brain metastatic tumor cells. Thus, targeting CCL2 is a potential clinical application in treating brain metastases.**

**Zhang L, Zhang S, Yao J, et al. 2015. *Nature* 527(7576):100-104.**

# Breast Cancer Research Semipostal Program

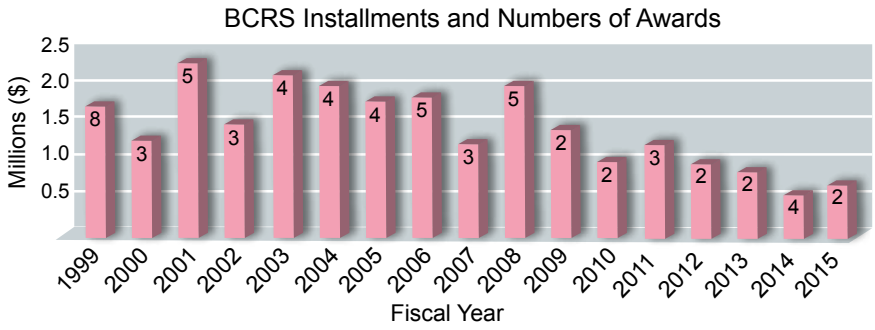

## Program History

As a result of the efforts of breast cancer advocates, the Stamp Out Breast Cancer Act (Public Law 105-41) led to the U.S. Postal Service's issuance of a new first-class stamp, the Breast Cancer Research Semipostal (BCRS), in 1998. It was the first semipostal in U.S. history. Net revenues from sales of the BCRS, which currently costs 60 cents, are provided to two designated funding agencies, the DoD BCRP and the NIH, to support breast cancer research. By law, 30 percent is allocated to the DoD BCRP, and 70 percent of the total amount raised is allocated to the NIH. The Breast Cancer Research Stamp Reauthorization Act of 2015 reauthorized the stamp through 2019.

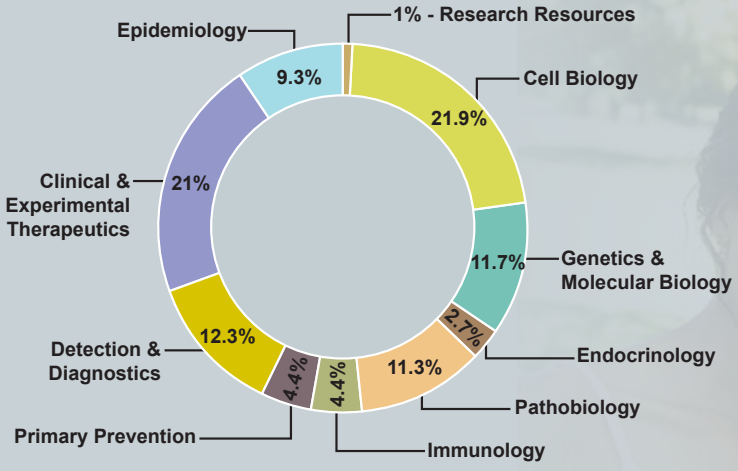
| Total Proceeds from BCRS (through FY15) | $24,140,455.70 |
|---|---|
| Research | $22,973,598.25 |
| Management Costs | $1,166,857.45 |

## Research and Management Costs

Breast cancer stamp funding received by the BCRP between FY99 and FY15 has been used to fully or partially fund 61 awards under three award mechanisms: the Idea Award, Synergistic Idea Award, and Breakthrough Award Funding Level 1. These award mechanisms support innovative, high-risk, high-reward research that could lead to major advancements in breast cancer. Applications funded through the BCRS Program were reviewed and recommended for funding according to the two-tier review system implemented by the DoD BCRP. An evaluation of the awards funded through the BCRS Program shows that the projects encompass a diversity of research areas.




## FY99–FY15 BCRS Research Portfolio (% dollars invested)




## Hazardous Air Pollutants and Breast Cancer: An Unexplored Area of Risk

**Peggy Reynolds, M.P.H., Ph.D., Cancer Prevention Institute of California**

Breast cancer rates vary dramatically by geographic region, suggesting that environmental factors could play a role in the etiology of breast cancer. With support from an FY09 Idea Award funded by the BCRP and the BCRS, Dr. Peggy Reynolds quantitatively examined the relationship between modeled ambient exposure to hazardous air pollutants (HAPs), including potential carcinogens or estrogen disruptors, as well as breast cancer incidence, using a large prospective cohort of women living in California. A significant increase in breast cancer risk was observed for women residing in areas with high estimated concentrations of propylene oxide and vinyl chloride. Several other HAPs were also associated with increased incidence of breast cancer, based on hormone receptor status. Estrogen receptor-positive or progesterone receptor-positive (ER+/PR+) tumors were associated with higher ambient levels of acrylamide, benzidine, carbon tetrachloride, ethylidene dichloride, and vinyl chloride, while ER-/PR- tumors were associated with higher ambient levels of benzene. Among the estrogen-disrupting HAPs, higher levels of cadmium and inorganic arsenic were associated with ER-/PR- tumors. These findings suggest that environmental exposure to air pollutants could contribute to an increased risk of breast cancer in some women, potentially by operating through a hormonal pathway.

Garcia E, et al. *Intl J Environ Health Research*, 2014 Aug; 24(4):363-77
Garcia E, et al. *Environmental Health* 2015 January; 14:14

## Noninvasive Label-Free Detection of Micrometastases in the Lymphatics with Ultrasound-Guided Photoacoustic Imaging

**Geoffrey Luke, Ph.D., Thayer School of Engineering, Dartmouth College**

Dr. Geoffrey Luke received an FY13 Breakthrough Award funded by the BCRP and BCRS to develop a combined ultrasound/photoacoustic (US/sPA) imaging device to detect micro-metastases in the lymph nodes. The standard method for determining whether cancer cells have left the primary tumor is sentinel lymph node (SLN) biopsy. However, this is an invasive procedure that exposes the patient to radioactive compounds and may require 2 or more weeks to obtain results.

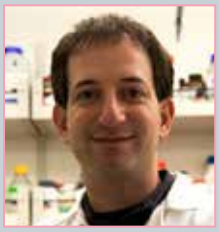
Dr. Luke's goal is to transform metastasis detection with a breakthrough system that requires no external contrast agent, delivers no ionizing radiation, and can generate high-resolution images at a depth of several centimeters in real time. US examination of lymph nodes, combined with sPA imaging, may result in a sensitive, noninvasive clinical tool capable of depicting small metastases.

Dr. Luke is using the combined US/sPA imaging system to monitor the functional changes that occur with the onset of lymph node metastases. Dr. Luke previously found significant decreases in SLN blood oxygen saturation with increase in metastasis in an animal model of oral cancer, and current experiments in breast cancer are showing the same trends. Dr. Luke is now working to improve the sensitivity and specificity of his US/sPA system in preparation for human breast cancer studies.

Geoffrey P. Luke and Stanislav Y. Emelianov. *Radiology,* 2015. 277:435-442.

## A Strategy for Direct Chemical Activation of the Retinoblastoma Protein

**Seth M. Rubin, Ph.D., University of California, Santa Cruz**



The retinoblastoma (Rb) protein pathway, a tumor-suppressive network, coordinates cellular growth signals with cell cycle progression and is frequently altered in breast cancer cells. Rb regulates cell cycle progression by interacting with transcription factor E2F, keeping cell proliferation in check. Dr. Seth Rubin and his team undertook a novel approach to restore Rb pathway function. With support from an FY13 Breakthrough Award funded by the BCRS, Dr. Rubin sought to show for the first time that the Rb pathway could be reactivated through direct targeting of Rb to enhance its binding to E2F in the presence of upregulated cyclin-dependent kinase (CDK) 4/6 activity. Dr. Rubin's work used an elegant quantitative fluorescent polarization assay to demonstrate that a peptide was capable of increasing the binding affinity of phosphorylated Rb to E2F. The information obtained has the potential to open a new avenue of research on peptides or small molecules that specifically reactivate the Rb tumor suppressive pathway and bypass upstream CDK-dependent signaling to inhibit breast tumor cell proliferation.

Pye, C.R., et al. *ACS Chem. Biol.* 2016, 11: 1192-1197.

# Duchenne Muscular Dystrophy Research Program

## Program History

The Duchenne Muscular Dystrophy Research Program (DMDRP) was established in FY11, the result of passionate and tireless advocacy efforts. The initial congressional appropriation for DMDRP was $4M, and since that time, $20M has been appropriated to the program, including $3.2M in FY16. Over the past several years, the number of potential therapeutics in the development pipeline for Duchenne has significantly increased, with some moving forward to clinical trials and demonstrating promising results. To help support these current therapeutic development efforts, the DMDRP solicits projects focused in several areas, including cardiac studies, clinical studies, and novel interventions to improve clinical care and quality of life; assessment of clinical trial tools and outcome measures; and advanced therapeutic preclinical studies. The DMDRP aims to accelerate the transformation of promising therapeutic ideas into clinical applications and encourage new physician researchers to pursue careers in Duchenne research.

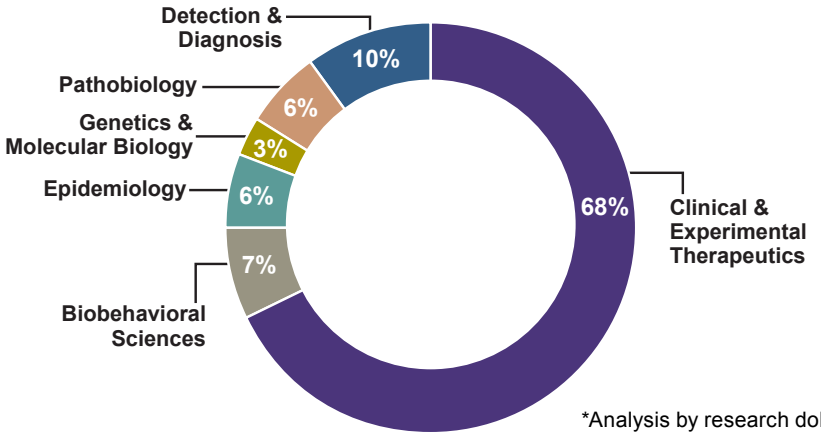
## Vision

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 the discovery and development of therapeutics, devices, and other interventions, and to promote their effective clinical testing

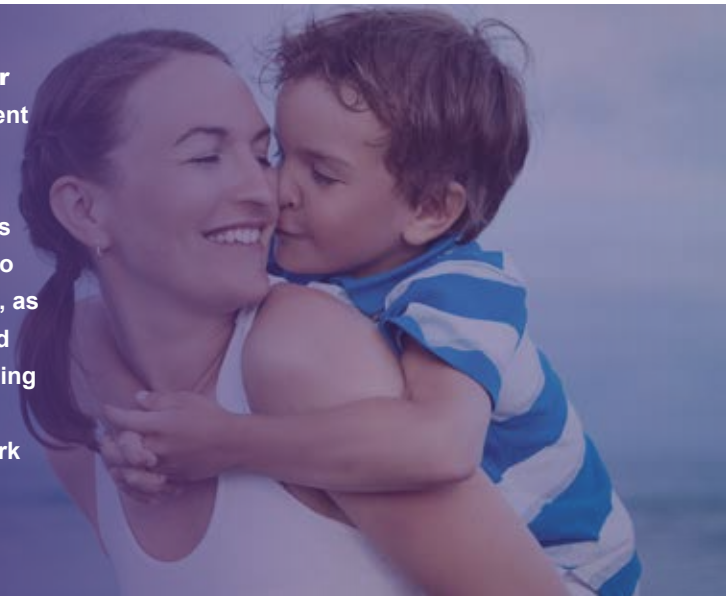
### FY11–FY15 DMDRP Portfolio by Research Areas*




*Analysis by research dollars.

**Robert McDonald, Consumer Peer Reviewer**

**"I was thrilled to see the dedication and commitment of this DoD program and the involvement of the consumers affected by this disease. The review process was thorough and professional, and it was gratifying as a consumer involved in the process to have my voice heard and respected. This program, as well as other peer review efforts I have participated in, gives my family a sense that we can and are doing something to help all the young men with DMD. It serves to give families real hope against a very dark and tragic diagnosis."**



## Research Accomplishments

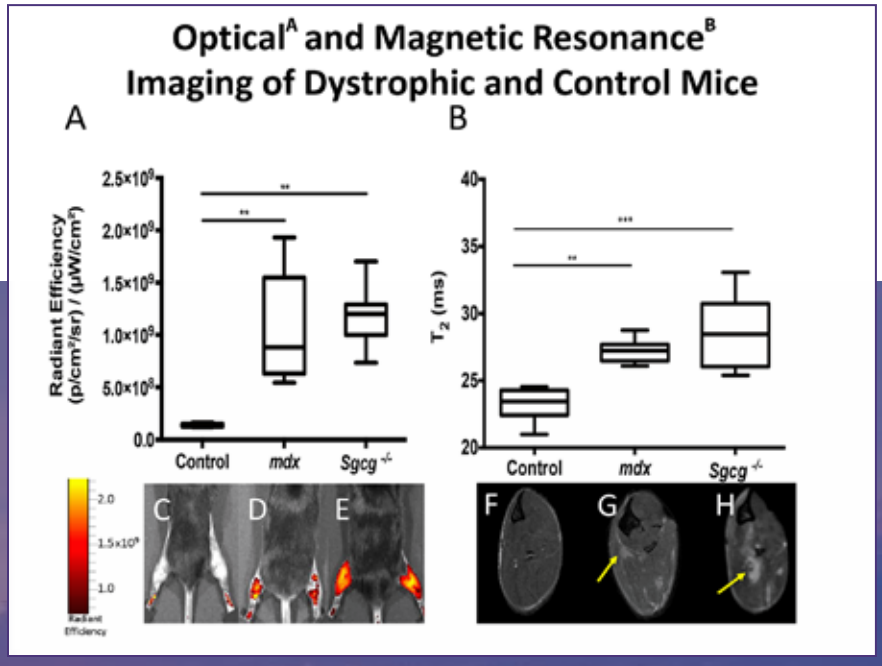
### Optical Imaging of Damaged and Dystrophic Muscle

**Glenn Walter, Ph.D., University of Florida**

Duchenne muscular dystrophy is an inherited disease that is caused by defects in the production of the structural muscle protein, dystrophin, which provides support and repair in normal muscle cells. The absence of dystrophin results in progressive skeletal muscle damage that limits mobility and eventually leads to cardiac and respiratory complications. While novel therapeutics within the Duchenne research community are showing promising results in animal and human studies, a major limitation is the lack of effective methods to measure changes in muscle integrity non-invasively, in real time, at low cost, without harmful radiation, and with minimal patient discomfort. Dr. Glenn Walter, using an FY11 DMDRP Investigator-Initiated Research Award, sought to develop a novel optical tool using a near-infrared (NIR) imaging technique to differentiate damaged muscle cells from rescued and normal muscle tissue.

Dr. Walter's work has demonstrated that NIR light, combined with magnetic resonance imaging (MRI), can be used to quantitatively image and assess muscle damage and non-invasively follow therapeutic interventions. Their studies have utilized murine models to optimize the use of NIR optical imaging (NIR-OI) and MRI to visualize damaged muscle using the contrast agent Indocyanine Green (ICG). These imaging techniques have been able to show improvements in muscle integrity resulting from gene therapy. Their work has explored the use of polylactide-coglycolide acid (PLA) polymer nanoparticles that contain ICG for enhanced imaging. These nanoparticles also have the potential to transport therapeutics, such as antisense oligonucleotides (AONs), for targeted drug delivery. Initial studies indicate the PLA-ICG nanoparticles have sustained in vivo imaging capabilities (up to 4 weeks) and show promise for prolonged release and delivery of therapeutic AONs. Their studies have indicated NIR-OI is more sensitive than MRI for detection of muscle damage in vivo. In addition, Dr. Walter's group is currently evaluating the translation of NIR-OI, using ICG in patients in a clinical trial with both Duchenne and healthy pediatric subjects. The goal of this study is to validate the potential of these optical imaging techniques to detect and quantify muscle damage in a population affected by Duchenne muscular dystrophy, as well as in a healthy population that has undergone acute muscle damage due to an exercise intervention.

The success of this work is integral to being able to develop and track the progress of targeted therapeutics in neuromuscular disorders, such as Duchenne muscular dystrophy. This imaging shows promise in assessing individuals for muscle damage in a non-invasive, safe, repeatable, objective, and quantifiable manner for closer disease monitoring and management.



# Epilepsy Research Program

## Program History

The DoD Epilepsy Research Program (ERP) was established in FY15 to address the critical need to understand the magnitude and underlying mechanisms of post-traumatic epilepsy (PTE), especially in Service Members and Veterans, while also benefitting the civilian community. With a total of $15M in congressional appropriations over the past 2 years, the ERP funds innovative research through the Idea Development Award mechanism, using two funding levels. Level I is intended to support research that is high risk and/or high gain. Level II is intended to support advanced studies that may be multidisciplinary in nature. Through collaborative efforts of academic scientists, subject matter experts, and advocates, the ERP's FY16 four Focus Areas have been established and are listed below.

## Vision

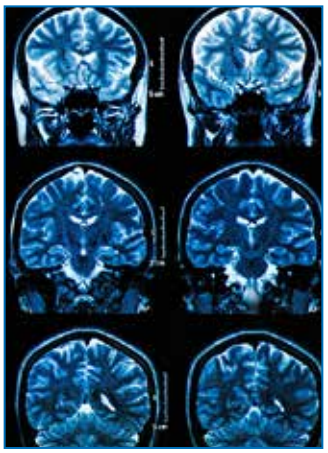
The ERP envisions a time when the causative links between TBI and epilepsy are understood and PTE is preventable

## Mission

The ERP's mission is to fund research to understand the magnitude, and the underlying mechanisms of PTE, especially in Service Members and Veterans

**Epidemiology:** Epidemiological characterization of PTE following traumatic brain injury (TBI), may include:

- Risk factors such as demographics, genetic factors, organic head injury factors, or type of insult
- Differentiation of PTE and Psychogenic Non-Epileptic Seizures (PNES)
- Outcomes including latency to epilepsy, morbidities and comorbidities, and mortality
- Pre-existing conditions including psychological and psychiatric risk factors



**Markers and Mechanisms:** Identification of markers or mechanisms (via clinical prospective or preclinical models) that address PTE, including early detection, diagnosis, prognosis, morbidity and comorbidity, mortality, and risk stratification.

**Models of PTE:** Development of new models or better characterization of existing etiologically relevant models for PTE, including repetitive TBI.

**Psychogenic Non-Epileptic Seizures:** Exploration of the epidemiology, mechanisms, risk factors, or markers of PNES subsequent to TBI. Preclinical research on non-pharmacological interventions is encouraged.

**CPT Karen Parko, M.D., U.S. Public Health Service, Ret., Inaugural National Director, VA Epilepsy Centers of Excellence**

**"The Epilepsy Research Program will play a critical role in elucidating and understanding epilepsy and its comorbidities as a consequence of traumatic brain injury. The programmatic panel is comprised of U.S. leaders in the field of epilepsy, representing a broad spectrum of stakeholders from the DoD, VA, NINDS, Academic Basic Science, nongovernmental research agencies, and epilepsy non-profit foundations. 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."**

## About the ERP Programmatic Panel

The Programmatic Panel is responsible for directing the overall mission and vision of the ERP. In addition to reviewing the Program's Mission, Vision, and Focus Areas, the Panel also makes recommendations to the CDMRP regarding investments for the ERP's research portfolio, based on the program goals and scientific peer review. While the Programmatic Panel does not re-review the technical nature of the proposals received in response to the ERP's Program Announcements, the Panel members serve a critical need in that they are directly responsible for identifying the best research investments for the ERP to meet the program's needs. The Programmatic Panel receives guidance from the ERP's peer reviewers and considers this guidance as it reviews applications and recommends which projects should be funded. In addition to peer reviewer comments, the Panel weighs the relevance of each proposal to both the ERP's goals and its portfolio composition, in order to maintain a well-balanced portfolio of research.

## Consumer Participation

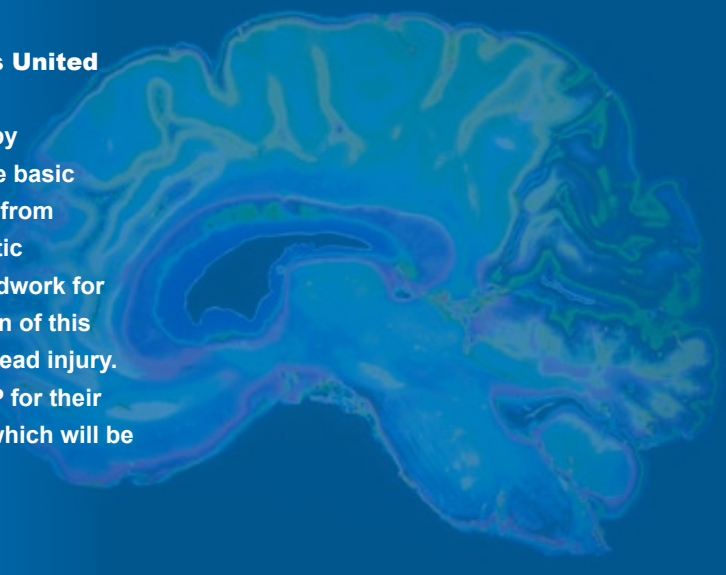
Consumers represent the voice and vision of individuals affected by PTE. Consumers for the ERP are persons with military service living with, or family members/caregivers of a person living with, PTE. (For more information, please go to cdmrp.army.mil.) The ERP incorporates consumers as active participants in virtually all aspects of program execution. Consumers work collaboratively with leading scientists and clinicians in setting priorities, reviewing proposals, and contributing their unique perspectives and a sense of urgency to program processes. Consumers also serve as liaisons between their constituencies and the scientific community, and increase awareness about the ERP in the consumer community.

## FY15 Awards

| | | |
|---|---|---|
| **Idea Development Award** | ***Level I*** | **John Wolf, Ph.D.,** University of Pennsylvania<br>*Diffuse and Focal Brain Injury in a Large Animal Model of PTE: Mechanisms Underlying Epileptogenesis* |
| | | **Jeanne Paz, Ph.D.,** J. David Gladstone Institutes<br>*Deconstruction and Control of Neural Circuits in Posttraumatic Epilepsy* |
| | | **Doodipala Reddy, Ph.D.,** Texas A&M University System Health Science Center<br>*Epigenetic Mechanisms of Posttraumatic Epilepsy* |
| | ***Level II*** | **Mary Jo Pugh, Ph.D.,** South Texas Veterans Health Care System<br>*The Epidemiology of Epilepsy and Traumatic Brain Injury: Severity, Mechanism, and Outcomes* |
| | | **Daniel Barth, Ph.D.,** University of Colorado at Boulder<br>*Major Reassessment of the Fluid Percussion and Controlled Cortical Impact Models of Posttraumatic Epilepsy* |

**Susan Axelrod, CURE | Citizens United for Research in Epilepsy**

**"The Epilepsy Research Program, by enhancing our understanding of the basic mechanisms of epilepsy stemming from traumatic brain injury (post-traumatic epilepsy), will help to lay the groundwork for more-effective treatments and—one day—even prevention of this serious and potentially life-threatening consequence of head injury. I applaud the work of the Department of Defense and ERP for their investment in research—the cornerstone of discovery—which will be so meaningful to our Service Members and Veterans."**



# Gulf War Illness Research Program

## Program History

DoD-funded research into Gulf War Illness (GWI) began in 1994 with the establishment of a Gulf War Veterans' Illnesses Research Program (GWVIRP) to study the health effects of Service Members deployed in the 1990–1991 Persian Gulf War. From FY94 to FY05, the GWVIRP was managed by the U.S. Army Medical Research and Materiel Command Military Operational Medicine Research Program (MOMRP). Research pertaining to GWI also was funded intermittently through the CDMRP's Peer Reviewed Medical Research Program (PRMRP), which supports selected military health-related research topics each fiscal year. The MOMRP shared management responsibility for the GWVIRP with the CDMRP in FY06, with separate $5M appropriations. Although Gulf War–related research was not funded in FY07, a $10M appropriation renewed the program in FY08, renamed the Gulf War Illness Research Program (GWIRP), to be managed fully by the CDMRP. From FY08 to FY15, the GWIRP has received a total of $124M in congressional appropriations. From these appropriations, the program has built a broad research portfolio of over 120 awards featuring clinical trials and basic research, as well as studies addressing chemical exposures and GWI symptomatology. In 2012, two major multidisciplinary, multi-institutional research efforts by leading GWI investigators were initiated to address specific aspects of autonomic dysregulation and neuro-inflammation in investigations spanning the range from basic research to clinical trials.

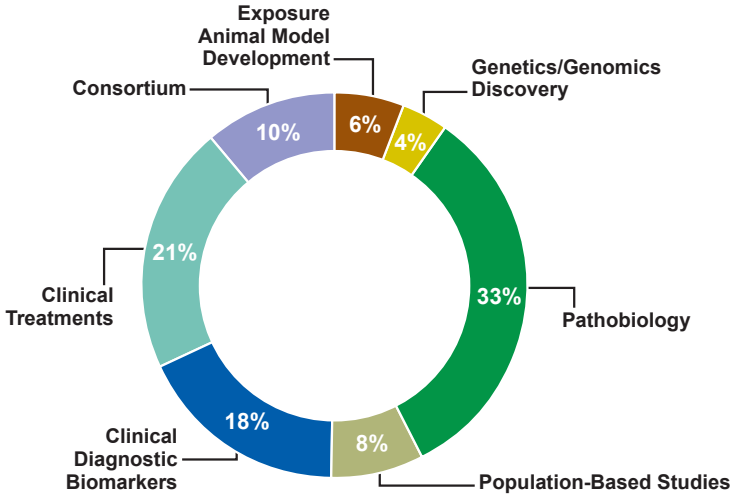
## Vision

Improve the health and lives of veterans who have Gulf War Illness

## Mission

Fund innovative Gulf War Illness research to identify effective treatments, improve definition and diagnosis, and better understand pathobiology and symptoms

## FY06–FY15 GWIRP Funding by Research Area




**Vera Roddy, Peer Review Panel Member, FY14–FY15**

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

## What is Gulf War Illness?

GWI is characterized by persistent symptoms such as widespread pain, cognitive difficulties, debilitating fatigue, gastrointestinal problems, respiratory symptoms, chronic headache, sleep problems, and other abnormalities that are not explained by traditional medical or psychiatric diagnoses. This complex set of chronic symptoms may affect as many as 250,000 veterans of the 1990–1991 Gulf War, out of the nearly 700,000 deployed to that region. The GWIRP focuses its funding on innovative projects that have the potential to make a significant impact on GWI, improving the health and lives of affected Service Members and their families.

### Defects in Cell Energetics in GWI

**Beatrice Golomb, Ph.D., University of California, San Diego**

Disruption of cellular energy production produces symptoms similar to those observed in GWI, such as fatigue, cognitive issues, muscle problems, gastrointestinal issues, and difficulty breathing. Therefore, Dr. Beatrice Golomb hypothesizes that mechanisms that affect cell energy, including mitochondrial alterations, may play an important role in GWI. In previous GWIRP studies, she found that phosphocreatine, which serves as an energy reservoir in muscles, is replenished more slowly after exercise in GWI patients than in healthy controls and that doses of the vitamin Coenzyme Q10 (CoQ10) improved GWI symptoms. In new, ongoing GWIRP studies, Dr. Golomb will be expanding and elaborating her previous study of energy production defects in a larger, geographically distinct Gulf War Veteran population. She is also employing a personalized-medicine approach to measure a number of energy-producing functions in each patient and formulate a partially personalized cocktail, including CoQ10 and other compounds, that address particular energy production defects identified in that patient. If successful, these studies provide hope for reducing some of the most common problems experienced by those suffering from GWI.

### MicroRNAs as Potential Therapeutic Targets in GWI

**Lisa Pierce, D.Sc., Tripler Army Medical Center**

Dr. Pierce used an established rat model of GWI to examine short-term and long-term effects of Gulf War-relevant chemical exposures and stress on neuroinflammation and altered microRNA (miRNA) expression in the central nervous system. miRNAs are a recently discovered, highly conserved, important class of small (~22 nucleotide), non-protein-coding RNAs that regulate transcription, messenger RNA stability, and protein expression levels of target genes. Dr. Pierce's most significant finding thus far has been the persistent increase in the expression of a specific miRNA, miR-124, in the hippocampus of GWI rats. Dr. Pierce believes in vivo inhibition of miR-124 function in the hippocampus could be a promising and novel therapeutic approach to improve cognition, emotion regulation, and neuroendocrine dysfunction in GWI. Dr. Pierce has received continued funding in an FY15 GWIRP Investigator-Initiated Research Award to further her research on the therapeutic potential of miR-124 inhibition in treating GWI.

### Lipid Metabolism as a Treatment Target in GWI

**Laila Abdullah, Ph.D., Roskamp Institute**

**Lipid metabolism can influence immune responses. Pesticides, to which GW veterans were exposed, can alter lipid metabolism. Dr. Laila Abdullah's team is focusing on lipid metabolism to identify novel therapies for GWI. In the first year of this project, Dr. Abdullah developed methods to detect lipid changes in an established mouse model of pyridostigmine bromide and permethrin exposure. Preliminary studies showed that exposed mice had low brain cardiolipin, a signature mitochondrial phospholipid that is required for electron transport and oxidative phosphorylation. She also observed low omega-3 fatty acids in the brains of exposed mice at a chronic time-point. Her team showed that short-term treatment with a natural lipid restored the brain phospholipid profile and reduced astroglia activation in exposed mice. This team is now determining whether long-term treatment with such therapies can reduce chronic symptoms and brain pathologies of GWI in their mouse model. The ultimate goal is to identify translatable therapies for treating GWI.**

# Joint Warfighter Medical Research Program

## Program History

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

Each year, a broad spectrum of research projects are considered for funding under the JWMRP. The projects align to the six Joint Program Committee (JPC) scientific domains represented in the DMRDP, including Medical Simulation and Health Information Sciences (JPC-1), Military Infectious Diseases (JPC-2), Military Operational Medicine (JPC-5), Combat Casualty Care (JPC-6), Radiation Health Effects (JPC-7), and Clinical and Rehabilitative Medicine (JPC-8).

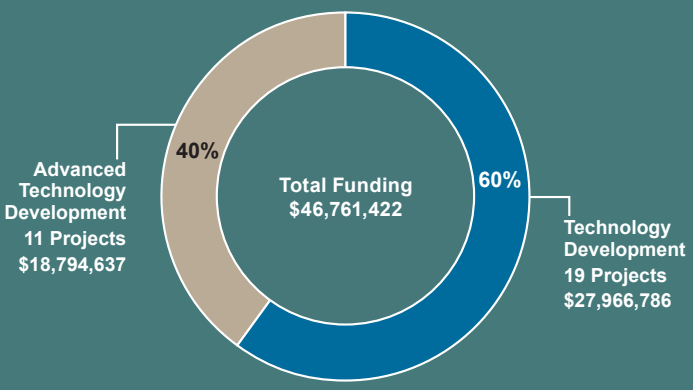
Congress first appropriated $50M for the JWMRP in FY12 and again in FY13, then later doubled the appropriation to $100M in FY14, followed by an additional $50M in FY15 and FY16. Because the overall goal of the program is to deliver a product for the DoD, the ratio of funding allocation over the past 3 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 through the FY12 JWMRP; 35 projects are aligned to the FY13 JWMRP; 46 projects are funded through the FY14 program; and 30 projects are funded in the FY15 program. The graph below depicts the program funding allocations for FY15.

## Vision

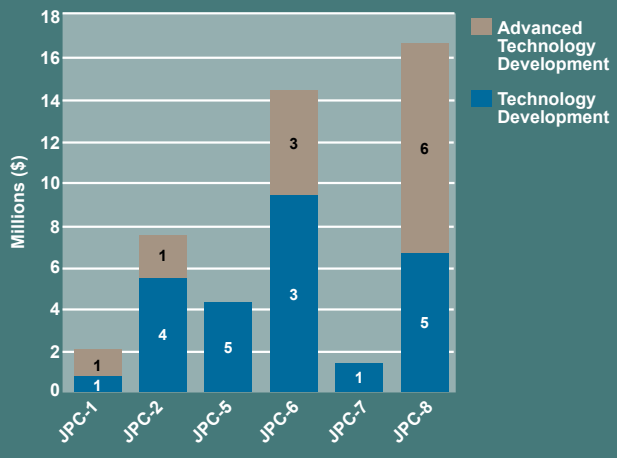
Move military relevant medical solutions forward in the acquisition life-cycle to meet the needs of Service members and other military health system beneficiaries

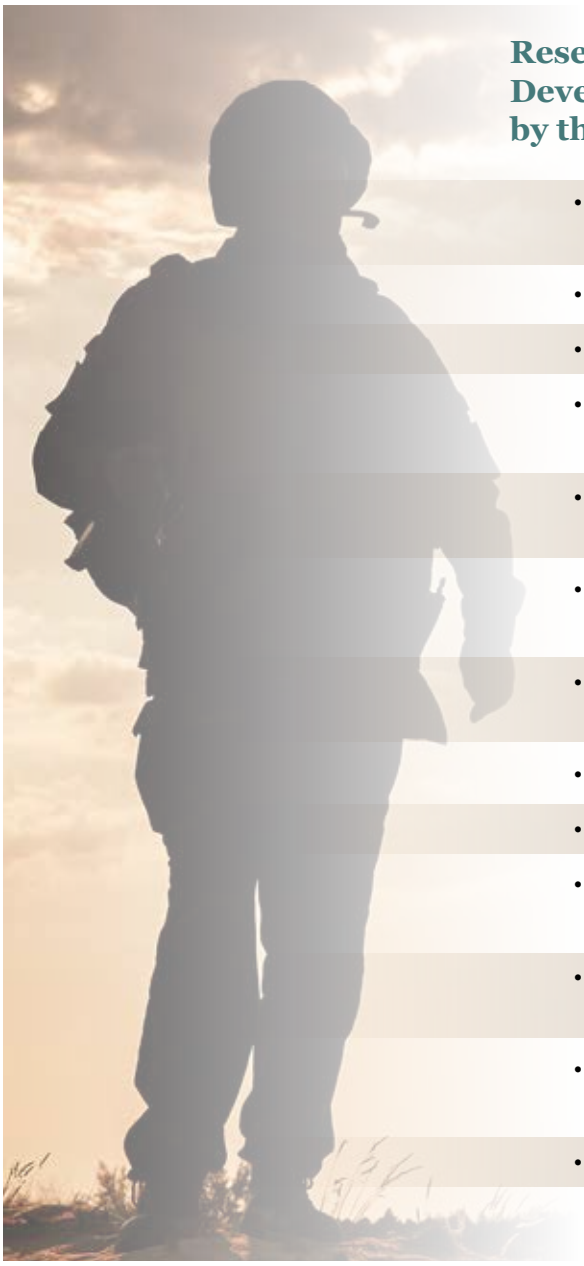
***The JWMRP is a dynamic program that facilitates the maturation of previous congressionally funded research efforts that demonstrate the potential to close identified military medical capability gaps.***

## FY15 Summary




## FY15 Final Funding Distribution





## Research and Product Development Efforts Funded by the JWMRP Include:

- Focused effort on improving cognitive and functional deficits after traumatic brain injury using virtual technology
- Intelligent tutoring system for emergency preparedness training
- 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 and evaluation of implantable nanosensors to monitor key physiological parameters of Warfighter health
- Development of a passive physiological monitoring system during medical evacuation
- 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
- Modifying and enhancing lower-extremity prosthetics to restore balance and locomotion
- Development of bioengineered corneas for transplantation

***By focusing on both early and advanced technology development, the JWMRP provides a pathway to transition products to military health care providers and the Warfighter.***

# Lung Cancer Research Program

## Program History

The Lung Cancer Research Program (LCRP) was established in FY09, and over the past 7 years, it has played a critical role in supporting high-impact, innovative research within the military and general public for risk assessment, prevention, early detection, diagnosis, and treatment for the control and cure of lung cancer. The dedicated efforts by lung cancer advocates to increase public awareness of this disease, as well as federal funding for its research, have led to total congressional appropriations of $101.5M to the LCRP, including $12M for FY16. To address the critical needs of the lung cancer research and patient community, the LCRP has developed seven areas of emphasis and requires that all applications to the LCRP address at least one of these areas, which include development of non- or minimally invasive detection tools; development or improvement of tools for early detection/screening; understanding the mechanisms of initiation and progression to clinically significant lung cancer; prevention and treatment; predictive and prognostic markers to identify responders and non-responders; understanding susceptibility or resistance to treatment; and, new for FY16, understanding contributors to lung cancer development other than tobacco. In addition, it is important to note that military personnel are at a higher risk of developing lung cancer than the general population due to increased rates of smoking, as well as an increased likelihood of exposure to environmental carcinogens during their service. To address our military's higher risk, all applicants to the LCRP's funding opportunities are required to describe how their research is relevant to the healthcare needs of military Service Members, Veterans, and their families.

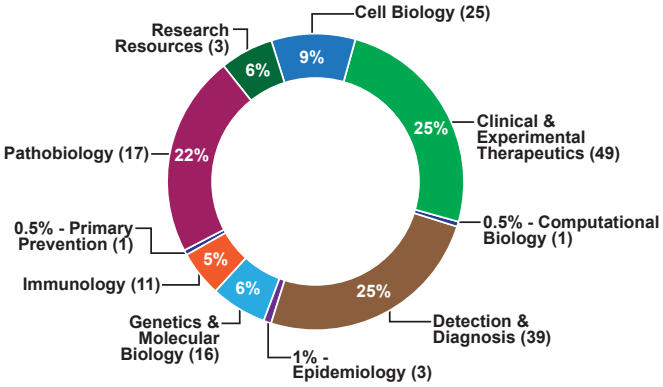
## Vision

Eradicate deaths from lung cancer to better the health and welfare of the military 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

## FY09–FY15 Portfolio by Research Area*




*Shown by percentage of dollars invested with number of awards in parentheses

**Karen Arscott, D.O., M.Sc,**
**Consumer Programmatic Panel Member**

**"As a physician who has seen lung cancer destroy so many lives, and as someone who has personally faced lung cancer twice, I had the feeling that lung cancer was forgotten. Being a member of the Programmatic Panel for the LCRP, I have a front row seat in seeing all of the effort being directed toward this major killer. It is more than gratifying to know that there is an army of researchers out there making serious progress in the screening, diagnosis, and treatment of lung cancer."**

## Encapsulated Solid-Liquid Phase Change Nanoparticles as Barcodes for Detection of Lung Cancer Biomarkers

**Ming Su, Ph.D., Northeastern University**

Through the funding provided by the Lung Cancer Research Program Concept Award, Dr. Ming Su of Northeastern University has established a novel approach for biosensing that is applicable to lung cancer, other cancers, and infectious diseases. In this biosensing approach, the thermal properties of phase-change nanoparticles can be used as reporting probes for biomarker detection.

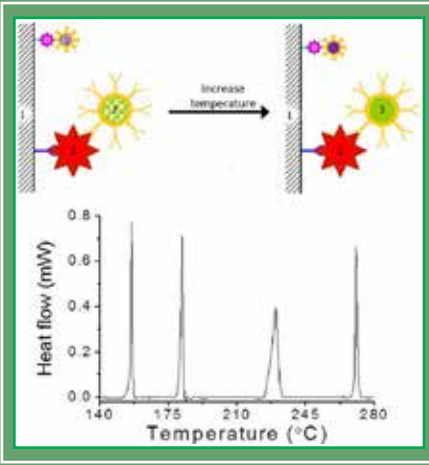
Early and accurate detection of lung cancer is crucial for effective treatment planning, maintenance of the disease, and survival. Researchers have found several potential biomarkers that could be used for early detection of lung cancers. Many of these, however, are not effective; have low concentrations; vary in presence and concentration at different stages of lung cancers; and/or require laborious sample preparation that may result in contamination, alteration, and/or loss. As a result of these challenges, no lung cancer screening methods that use validated biomarkers are clinically available today. A sensitive, accurate, simplified screening process remains stubbornly elusive.

Responding to the LCRP's FY09 area of emphasis addressing screening deficiency, Dr. Ming Su proposed a method that can screen multiple biomarkers, while supplying critical sensitivity with minimized time, effort, and resources. Dr. Su has focused his research largely on nanomaterial applications within medicine, especially thermal biosensor tools for screening of diseases. His preferred method uses a novel biosensor that can incorporate nanoparticles with unique thermal properties to screen for combinations of biomarkers.

With funding from the LCRP, Dr. Su and his team investigated the use of solid-liquid phase-change nanoparticles to detect multiple cancer biomarkers. The team succeeded in using a panel of nanoparticles made up of either metals or a mixture of metal and alloy to simultaneously detect four distinct proteins: rabbit IgG, human IgG, prostate specific antigen, and biotin. Nanoparticles first bind to according antibodies, and then are captured onto an antibody-modified plate after forming a sandwiched complex with antigens. The nanoparticles can be readout using differential scanning calorimetry, wherein the melting peak position and peak area reflect the presence and concentration of biomarkers. Although this method is still a work in progress, these biosensors can potentially revolutionize early detection of not just lung cancer, but other cancers as well—they are capable of measuring multiple proteins at a protein concentration range of up to four orders of magnitude above baseline. This sensitivity is important, since cancer biomarker protein concentration within plasma and serum can exceed 10 orders of magnitude, making it very difficult to accurately detect individual protein concentration, let alone multiple proteins.

Since completing the Concept Award, Dr. Su's team has continued to optimize thermal nanoparticle biosensor for early detection of cancer, hoping to achieve sensitive detection of biomarker concentrations within the range of 6 to 11 orders of magnitude. Dr. Su accredited much of his early professional development to receiving this Concept Award, noting that this project steered him toward a focus in nanomedicine. His group has expanded their efforts to using nanoparticles as concentrators of chemotherapy and radiation therapy, improving penetrating power and efficacy at low doses and eliminating bacteria without triggering drug resistance.

Dr. Su's dedication to advancing cancer screening tools is not limited to his own group's research. He is a guest editor for *Nanomaterials'* special issue, "Nanomaterials for Biosensing Applications," a collection of articles sharing nanomaterials' evolving biosensors for improved detection of diseases, inclusive of cancer. This special issue has published nine papers from September 2015 through March 2016, all of which portray unique methods. These various approaches provide optimism that improved screening tools for lung cancer and other diseases are closer to reality.




**Dr. Su's methods allow for detection of protein biomarkers (2) through binding onto an antibody-tagged plate (1) and thermal readouts of phase change nanoparticles (3). By pairing specific types of nanoparticles to different types of protein biomarker, it is possible to determine the type and concentrations of multiple biomarkers in a single assay.**

# Military Burn Research Program

## 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 Combat Casualty Care Research Program (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 U.S. Service Members, Veterans, and those within the general public at large who sustain burn injuries. The funded research is expected to benefit both the military and civilian communities.

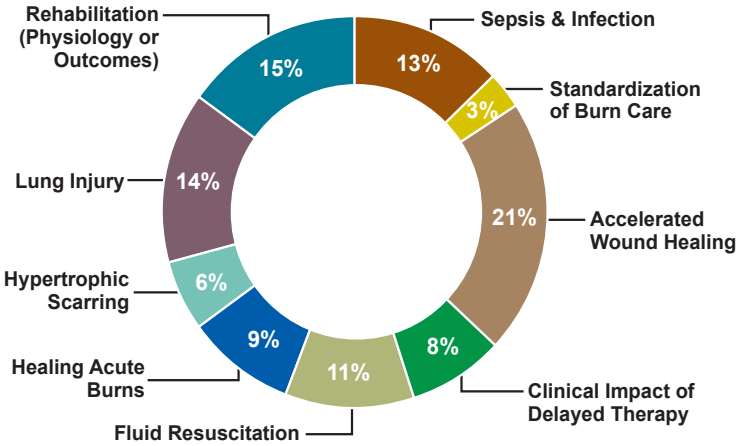
## Vision

Deliver the best combat burn trauma care to improve health and performance outcomes for the Warfighter

## Mission

Identify and address the traumas of burn, especially those combat-related injuries that affect the military population

## MBRP Portfolio (% based on total dollar amounts)




[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.

**Kevin K. Chung, M.D., FCCM, FACP LTC, MC, USA. Director of Research (Interim), U.S. Army Institute of Surgical Research.**
**"Severe burn is a devastating injury associated with a high risk of death, suffering, and permanent disability among our combat wounded. The Military Burn Research Program is a vital link between advances in burn trauma research and improved functional survival for future Warfighters who sustain this type of injury."**

## Working to speed recovery and improve the Quality of Life of our Soldiers

### Early Exercise in the Burn Intensive Care Unit Decreases Hospital Stay, Improves Mental Health and Physical Performance

**Oscar E. Suman, Ph.D., The University of Texas Medical Branch at Galveston (UTMB)/Shriners Hospitals for Children-Galveston**

Prolonged stays in the Burn Intensive Care Unit (BICU) are typically accompanied by inactivity among patients, resulting in increased muscle loss/weakness; decreased work/exercise capacity; impairment of cardiovascular/cardiopulmonary function; altered hematologic function, musculoskeletal structure, thermoregulation, and immune function; and abnormal psychosocial and neuroendocrine function. All of these factors complicate rehabilitation and lead to longer recovery times and delayed return to normal function, as well as a decreased quality of life. With a FY13 MBRP award, Dr. Suman and his team are characterizing the variable, vague, and unstructured standard of care (SOC) exercise guidelines for BICUs across the United States. Subsequently, compared to SOC alone, his team will determine whether a personalized, structured, and quantifiable exercise program, in addition to the SOC, would improve burn recovery. Bringing together four world-class burn units, they have begun a trial to determine whether their quantifiable exercise program, called MP10, will have a positive impact on lean body mass, cardiopulmonary and muscular endurance, length of stay in the BICU, ventilator use, length of hospitalization, and overall quality of life. If MP10 proves successful, this project will produce early mobilization/exercise protocols that will aid in the rehabilitation of burn patients and restore physical and psychosocial function to affected individuals.

### The Phases of Illness Paradigm: A Checklist-Centric Model to Improve Patient Care in the Burn Intensive Care Unit

**LTC Jeremy Pamplin, M.D., U.S. Army Institute of Surgical Research**

Burn critical care is complex and challenging. When treating patients, clinical teams operate collectively with fragmented and/or sporadically distributed information. Too often, this leads to medical errors and communication failures. Unlike research in other critical care environments, where checklists have been found to standardize supportive care elements, very little research has been published looking at the benefits of utilizing checklists to unify burn critical care teams. With an FY12 MBRP award, LTC Pamplin initiated a project to determine whether a checklist centric model, called “The Phases of Illness Paradigm” (POIP), would improve a healthcare team’s understanding of patient conditions and care priorities in order to enhance the quality of care in the BICU. Early results from this investigation have shown that, even when presented with the same information, clinicians caring for the same patient often have widely varying opinions about patient condition. Without being a burden, the introduction of POIP tools has improved synchronization and prioritization of patient care and increased team member agreement about a patient’s condition. Upon completion of this project, LTC Pamplin’s team expects to have a full understanding of the BICU work domain in terms of patient condition, progress, and dependent clinician behaviors. Additionally, the team expects to create a new, validated checklist that would support the daily duties of BICU clinicians across the nation.

# Multiple Sclerosis Research Program

## Program History

Multiple sclerosis (MS) is a degenerative, chronic inflammatory disease of the central nervous system (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 MS patient population. 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 2.1M 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 $39.1M has been appropriated to the program, including $6M in FY16.

## Vision

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

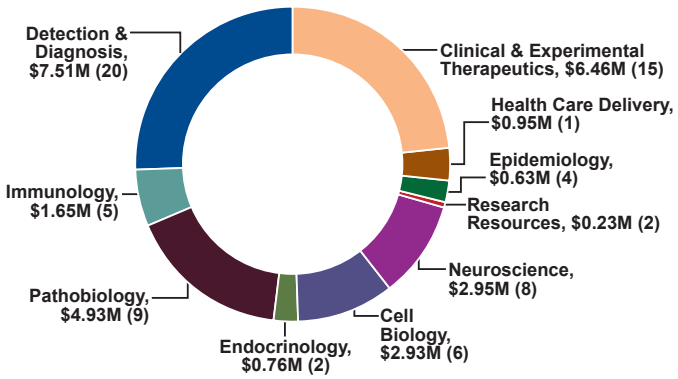
## Mission

To support pioneering concepts and high impact research relevant to the prevention, etiology, pathogenesis, assessment, and treatment of multiple sclerosis

## FY09–FY15 Research Portfolio

Through FY15, the MSRP has funded 72 awards, supporting topic areas such as exploration of highly innovative new concepts or untested theories; development of readily accessible, cost-effective, validated analytical methods; conceptually innovative, high-risk/potentially high-reward research; multidisciplinary research collaborations; development of translational research collaborations among clinicians and research scientists from within and outside the MS research field to accelerate the movement of promising ideas in MS research into clinical applications; and pilot clinical trials to investigate innovative interventions that could potentially have a profound impact on the management of MS symptoms.

## FY09–FY15 Portfolio by Research Area (numbers of awards)




**Stephanie Buxhoeveden, Consumer Peer Reviewer**

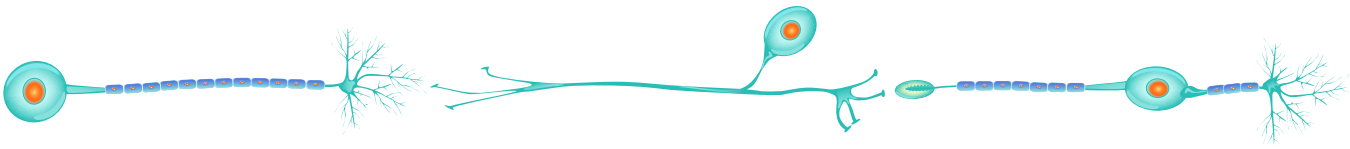
"My experience with the MSRP was great! During the peer review meeting, it was so interesting to be able to speak with such bright and distinguished panelists, and I really enjoyed the review process itself. I felt the opinions of the consumer peer reviewers added a lot of value and were an extremely important part of the process. I am so inspired by how many intelligent, passionate people are working to find solutions. I feel confident that, because of them, we are closer than ever to figuring out what causes MS, finding better treatments, and even finding a cure."

## Promising Therapeutic Reverses Chronic Demyelination and Prevents Axon Loss in a Mouse Model of Progressive MS

**David Pleasure, M.D., University of California, Davis**

Currently available therapies for MS patients, while effective in diminishing the incidence of relapses, do not prevent progressive neurological disability. Pigmentary epithelium-derived factor (PEDF), a multifunctional protein with neurotrophic properties, has been used safely to treat retinal diseases in humans. With an FY11 MSRP Idea Award, Dr. Pleasure found that recombinant PEDF enhanced the survival and regeneration of myelin-producing cells, oligodendrocytes, in a mouse model of MS. Furthermore, intravenous administration of the recombinant PEDF delayed the onset and decreased the peak severity of MS, as well as diminished long-term spinal cord dorsal axon loss and neurological deficits in this model system.

Sohn J, Orosco L, Guo F, et al. 2015. The subventricular zone continues to generate corpus callosum and rostral migratory stream astroglia in normal adult mice. *J Neurosci* 35(9):3756-3763.



## New Methods to Detect Abnormalities in the Cortical Gray Matter of MS Patients

**Seth Smith, Ph.D., Vanderbilt University Medical Center**

Although clinicians use Magnetic Resonance Imaging (MRI) techniques to diagnose and monitor treatment in MS, they cannot detect lesions that may occur in the gray matter (GM) of the brain, an area directly linked to cognitive impairment in MS. With an FY12 MSRP Idea Award, Dr. Smith developed a battery of quantitative MRI methods with sufficient resolution and sensitivity to characterize cortical GM in both healthy volunteers and patients with MS. Using advanced MRI techniques, Dr. Smith and his team were able to identify areas of increased and decreased functional activity that are specific to MS patients. Additionally, they have begun to characterize gray matter myelin and biochemistry. They also developed an extensive database of neuropsychiatric evaluation assessments for patients with MS and demonstrated the existence of differences compared to healthy volunteers. Dr. Smith's new technology has been used in multiple countries and patient populations.

Dula AN, Pawate S, Dortch RD, et al. 2015. Magnetic resonance imaging of the cervical spinal cord in multiple sclerosis at 7T. *Mult Scler*; 2015 Jul 24 epub ahead of print.

**Jonah Chan, Ph.D., University of California at San Francisco, Programmatic Panel Member**

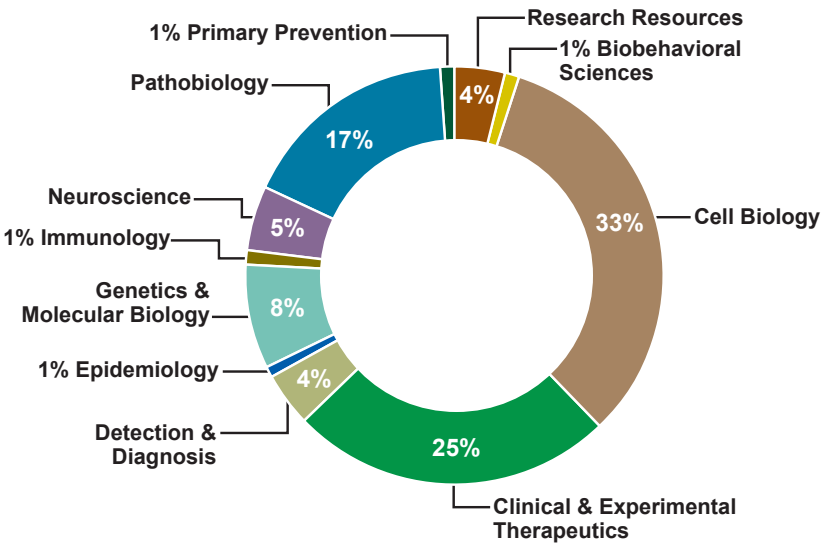
**"**The MSRP stands out from other MS funding agencies in that it actively attempts to address unmet needs in the research community from year to year. This past year, the Programmatic Panel unanimously recommended focusing on the symptomatology of MS, especially as many patients with MS live with symptoms caused by prior injury that existing therapies fail to address. In MS research, we've seen huge success in the development and deployment of treatments that tackle the immune dysregulation that seems to underlie injury in the disease. Many funding agencies are now also focusing on regeneration and repair for progressive patients. While these approaches are all important, the CDMRP took an imaginative approach to helping tackle MS. The MSRP provides vital funding to build and develop translational research programs. This, in turn, brings basic scientists and clinical researchers together and also encourages researchers who have not previously been involved in MS research. As a member of the Programmatic Panel, it has been especially gratifying to help grow research that may improve the lives of MS patients. Contributing in this manner is both a privilege and responsibility.**"**

# Neurofibromatosis Research Program

## Program History

The Neurofibromatosis Research Program (NFRP) was established in FY96 when the efforts of neurofibromatosis (NF) advocates led to a congressional appropriation of $8M. Since that time, $302.85M has been appropriated to the program, including $15M in FY16. 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 351 awards spanning basic, clinical, and population-based research.

### FY10–FY15 NFRP Portfolio by Research Area




## 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 those diseases

**Sharon Loftspring, Consumer Peer Reviewer**

**"**I served as a consumer reviewer of the grant proposals submitted for NF research 3 times since 2005. The experience has been invaluable to me - not only is the process informative about the happenings in the medical research arena, but it is rewarding to know that my opinion is valued.**"**

**Frank Buono, Consumer Advocate Peer Reviewer**

**"I was diagnosed with NF2 at the age of 9 years old, subsequent to my father's diagnosis of the same condition in his early 40s. The disease has affected me and my family in many ways – financially, emotionally, physically, and tragically. I highly recommend that individuals afflicted with his disease get involved and become consumer advocates. I cannot begin to describe how important it is for an individual suffering from this disease to become actively involved – and there is no better place than this organization to start."**

**David H. Gutmann, M.D., Ph.D., Washington University**

Neurocognitive impairments, including deficits in attention, function, language, and visual perception, have been reported in as many as two-thirds of children with neurofibromatosis type 1 (NF1). Dr. David Gutmann has developed an Nf1 genetically engineered mouse (GEM) model of optic glioma in order to study learning and behavioral abnormalities and to test potential therapies that may improve these abnormalities. With support from an FY09 NFRP Investigator-Initiated Research Award, Dr. Gutmann has found that the NF1 GEM strains display cognitive impairments that mirror those seen in children with NF1, including abnormal exploratory behaviors and spatial learning and memory deficits. Upon investigation into the causal mechanism(s) underlying these abnormalities, Dr. Gutmann discovered that reduced brain dopamine levels are responsible for these deficits. The neurocognitive assessments in NF1 GEM strains by Dr. Gutmann's research team have provided important insights into the behavioral abnormalities that occur in children with NF1 and support the use of dopamine-restorative agents to improve these defects. Furthermore, Dr. Gutmann has determined that these neurocognitive defects and dopamine signaling dysfunction are sex-dependent in mice, suggesting that sex may be an important prognostic factor for the neurocognitive impairments in children with NF1. These results also highlight the ability of NF1 GEM strains to serve as platforms for the discovery, development and testing of drugs to improve these cognitive and behavioral defects.

**Duojia Pan, Ph.D., Johns Hopkins University**

With support from a CDMRP FY09 NFRP Investigator-Initiated Research Award, Dr. Duojia Pan and his research team sought to use Drosophila to identify downstream genetic pathways controlled by Merlin. Through this work, Pan and his team revealed multiple layers of evidence linking Merlin to the Hippo (Hpo) genetic signaling pathway, an important signaling pathway in cancer development. The Hippo pathway involves a signaling cascade of genes, including Hpo, Warts (Wts), and YAP. First, they discovered that YAP, which is elevated in many human cancers, genetically interacts with Merlin, and the two genes function antagonistically to regulate mammalian tissue growth. Second, they showed that a protein complex, which consists of Kibra, Merlin, and Expanded, regulates Hpo signaling by targeting the Wts protein, and these proteins cooperate with each other to suppress tumor formation. Dr. Pan currently has an FY13 NFRP Investigator-Initiated Research Award to continue these studies. Research supported by this award will use the molecular data identified in his Drosophila studies to develop targeted therapies against NF2. Dr. Pan plans on testing an inhibitor of YAP that was identified in his laboratory, as well as identifying additional targets and potential inhibitors against those targets. These are the first studies to test drugs that specifically target the Merlin gene pathway and may lead to much-needed therapeutics for the treatment of NF2.

**Kathryn North, M.D., Children's Hospital at Westmead, Sydney, Australia**

**NF1 affects 1 in 3,000 individuals and is characterized by physical manifestations, including changes in skin pigmentation (café-au-lait spots) and the growth of benign tumors called neurofibromas usually located on or just under the skin. Dr. North received an NFRP FY03 Investigator-Initiated Research Award to identify and characterize early predictors of cognitive dysfunction in NF1 and, subsequently, to develop a screening tool for health professionals to assist in the early identification of cognitive deficits. To accomplish the goals of the study, Dr. North and her team followed children with NF1 from infancy to 7 years of age and evaluated their neurodevelopment and cognitive functioning over this period. They recently published some of their NFRP-funded results, including a longitudinal study of the cognitive development and behavior of young children with NF1 in the April 2015 edition of the *Journal of Pediatrics*. Dr. North and colleagues showed that mental development scores at 30 months of age had a greater influence on predicting later intelligence at 40 months of age than the mental development score at 21 months of age. They also found that, over time, children with NF1 consistently displayed significantly lower cognitive functioning than healthy controls.**

# Orthotics and Prosthetics Outcomes Research Program

## Program History

Limb deficit is one of the most debilitating traumatic injuries suffered by U.S. military personnel. Recent advancements in commercially available orthotics and prosthetics have dramatically improved device capability; however, an urgent need remains 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 goal of the OPORP is to improve our understanding and ultimately advance 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 policymakers.

## Vision

Helping our Warfighters achieve the highest possible quality of life through the advancement of revolutionary amputee and human performance related research

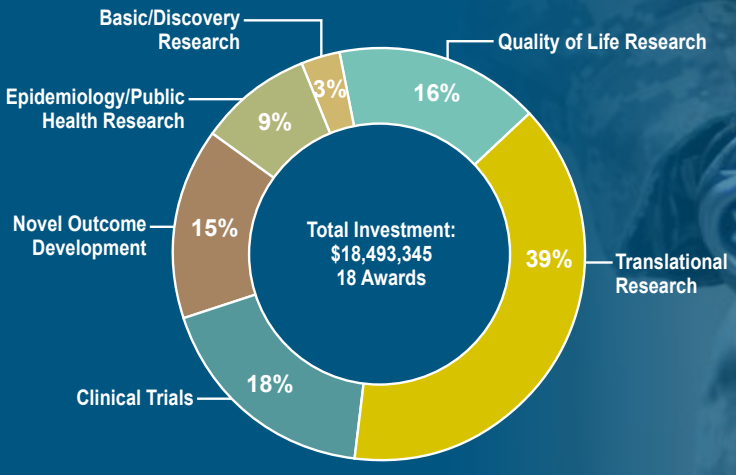
## Mission

Advance research towards more effective prosthetic and orthotic devices, treatment, rehabilitation, and the prevention of negative secondary health effects for military personnel, Veterans, and persons with injured limb function

**Sergeant Adam Kisielewski, USMC, Retired, Consumer Reviewer for OPORP**

**"**After being wounded during combat operations and living with multiple limb amputations, I can personally attest to the physical challenges of our severely injured Warfighters. The Orthotics and Prosthetics Outcomes Research Program funds some of the most relevant research aimed to improve the quality of life for those suffering from extremity trauma and ultimately helps our injured Service Members restore a greater level of independence. I am very proud to serve on the OPORP Programmatic Panel and help my peers overcome some of the physical challenges their injuries have presented.**"**

## FY14–FY15 Awards Summary by Dollar Amount and Investment Type



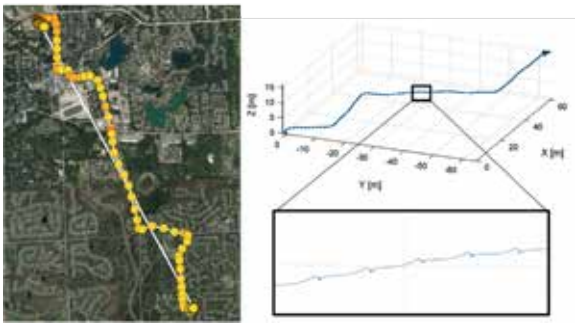
**Jennifer Johansson, Liberating Technologies, Inc.**

Liberating Technologies, Inc. (LTI), is both a research and development company and a manufacturer of components of upper- and lower- limb prosthetic devices for adults and children. Recently, Ms. Jennifer Johansson of LTI was awarded an FY14 OPORP award for her project, "Dynamic Corrective Force Device: A Balance Measure for Amputees." Ms. Johansson proposes to develop a microprocessor-based system of sensors, including pressure-sensing insoles that will dynamically sense the centers of pressure and gravity of patients using lower-limb prostheses. This will enable clinicians to assess prosthetic function during the daily activities of amputees and provide an evidentiary basis to help guide prosthetic selection for a wide range of activities. It will also enhance the ability to monitor the performance of patients and prostheses as lifestyle and daily needs change and evolve.

(Left) Prototype insole, showing multiple integrated pressure sensors. (Right) Prototype position sensor.

**Deanna Gates, Ph.D., University of Michigan**

Dr. Deanna Gates received an FY14 OPORA Level I award for "Determining the Potential Benefit of Powered Prostheses." This study is designed to join gait analysis with metabolic testing and activity monitoring in order to monitor function and mobility by comparing the BiOM Powered Ankle to standard clinical lower-leg prostheses without powered ankles. The study will employ a cross-over design, so that each patient will be able to personally experience the effect of a powered prosthetic in their daily lives and activities. Preliminary data show reduced muscle activity over the normal gait cycle for the gastrocnemius on the injured leg and the gluteus medius and the rectus femoris on the intact leg when using the powered ankle. It is not yet known whether this energy savings will translate into increased time to fatigue or increased activity for the average healthy patient. Dr. Gates has captured pilot data for a single patient and produced heat maps of intensity and location of activity for analysis to allow individual comparisons in the amount and types of activities performed in normal daily life. The data provided as part of this work will provide clinicians with a wealth of information to guide future prosthetic prescriptions based on patient lifestyles and daily needs.



Left Figure showing location and activity intensity (darker colors are higher intensity activities). Right Figure showing individual steps that the person takes throughout the day captured from an inertial measurement unit (IMU) on the foot. Data is shown for about 2 minutes of walking on an inclined surface. Dots represent when the foot contacts the ground.

## Focus Areas

***Focus areas for FY16 Orthotics Outcomes Research Award or Prosthetics Outcomes Research Award applications include:***

- **Lack of short- and long-term evidence for existing support and reintegration strategies following neuromusculoskeletal injury and a need for new evidence-based support and reintegration strategies**
- **Limited current technologies, including prosthetics and orthotics, for the rehabilitation or replacement of function that optimize patient interaction, usability, and durability**
- **Limited ability to predict, prevent, and mitigate development of secondary health deficits following neuromusculoskeletal injury**
- **Limited understanding of the management of patient rehabilitation strategies throughout the rehabilitation process following neuromusculoskeletal injury**
- **Lack of validated metrics that effectively assess initial presentation, rehabilitation, and reintegration following neuromusculoskeletal injury**

# Ovarian Cancer Research Program

## Program History

The DoD Ovarian Cancer Research Program (OCRP) was established in 1997 to define and address the critical research gaps facing the ovarian cancer community. The OCRP is the second-leading funder of ovarian cancer research in the United States. With $256M in congressional appropriations between FY97 and FY15, the OCRP has funded 372 research awards, resulting in over 1,200 peer-reviewed publications, nearly 100 patent applications, and high-impact advances in the prevention, screening, diagnosis, and treatment of ovarian cancer. The OCRP has transformed the landscape of ovarian cancer to the benefit of patients everywhere.

The success of the OCRP can be attributed to the synergistic efforts of many talented and dedicated individuals. A hallmark of the OCRP is the partnership of ovarian cancer survivors with scientists and clinicians, all of whom work together to set program priorities, design funding opportunities, evaluate research applications, and identify high-impact, innovative research that will lead to the elimination of ovarian cancer. The disease survivors lend their unique perspectives on the human dimension of the disease to support research that reflects their community concerns, as well as those of the clinicians who treat them.

## Program Portfolio

In striving to achieve the vision of eliminating ovarian cancer, the OCRP designed an investment strategy that continues to emphasize high-impact translational research, innovation, unique partnerships, and career development for talented young investigators who are committed to studying this disease. The portfolios show the type of investments made by the OCRP in the development of ideas and the research areas targeted through FY15.

## Vision

Eliminate ovarian cancer

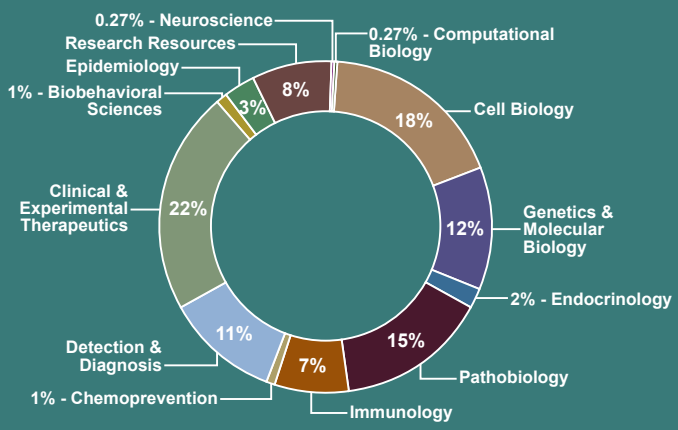
## Mission

To support patient-centered research to prevent, detect, treat, and cure ovarian cancer

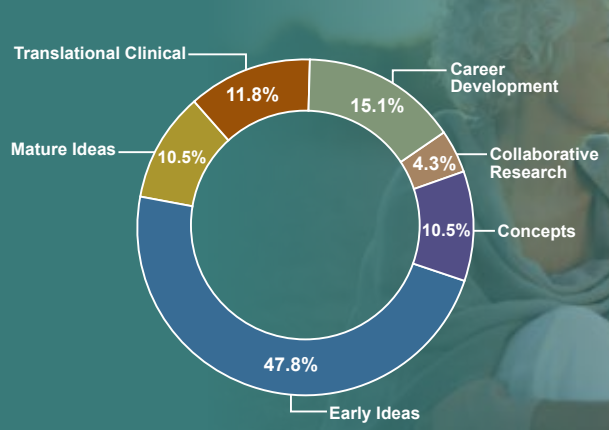
## Did You Know

- Ovarian cancer is the deadliest female reproductive cancer in the United States. Over the past 20 years, the OCRP has had a critical role in supporting high-impact, innovative research to address the issues and concerns unique to ovarian cancer.
- 1 in 70 women will develop ovarian cancer in her lifetime.
- Approximately 22,280 women will receive a new diagnosis of ovarian cancer in 2016, and 14,240 women will die from the disease this year (per the American Cancer Society).

## FY97–FY15 Portfolio by Research Areas




## FY15 Development of Ideas



## Trail-Blazing Research Funded During FY2015

**Malcolm Pike, Ph.D., Memorial Sloan Kettering Cancer Center** – The Multidisciplinary Ovarian Cancer Outcomes Group comprises a highly experienced, international team of Ovarian Cancer Association Consortium researchers. This team is studying genetic and epidemiological differences between long-term and moderate-term survivors of advanced-stage, high-grade serous ovarian cancer (HGSOC), in comparison to short-term survivors.

**Michael Birrer, M.D., Ph.D., Massachusetts General Hospital** – The Ovarian Cancer Consortium for Long-Term Survival team is working toward analyzing data to predict short-term versus long-term survival for patients with early-stage HGSOC. The results of this project will create an invaluable resource of genomic/biologic/proteomic data that are linked to quality of life and clinical data.

**Magdalena Plebanski, M.A., M.B.A., Ph.D, Monash University** – An existing drug, Sitagliptin (Januvia™), commonly prescribed to treat type II diabetes, may prove to be a novel therapy for epithelial ovarian cancer. A combination of standard chemotherapy and Sitagliptin will be tested in an animal model of HGSOC to determine whether this combination can act as a novel treatment for ovarian cancer.

**Panagiotis Konstantinopoulus, M.D., Ph.D., Dana-Farber Cancer Institute** – A collaborative effort within the OCRP Ovarian Cancer Academy is using novel strategies against a type of ovarian cancer harboring Cyclin E1 (CCNE1) amplification.

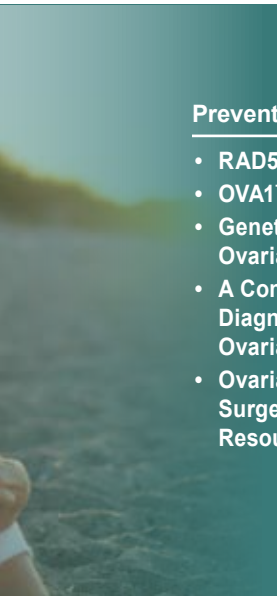
**Amy Skubitz, Ph.D., University of Minnesota, Twin Cities** – This work is focused on developing a non-invasive screening test that can be readily incorporated into a routine Pap test, allowing women to simultaneously receive screening for ovarian and cervical cancer.

**Rachel Miller, M.D., University of Kentucky** – Patients who receive chemotherapy for ovarian cancer sometimes experience a phenomenon called "chemobrain," a side effect of therapy that affects memory, attention, information processing, and thought organization. A clinical trial is currently enrolling ovarian cancer patients to understand chemobrain, with the goal of assisting physicians in timely diagnosis of this condition and delivery of treatment to alleviate symptoms.

**Gary Nolan, Ph.D., Stanford University** – This innovative research is analyzing a single cell with a technology called mass cytometry, which simultaneously measures protein expression, protein function, and the molecular signatures of primary ovarian cancer samples. To date, work on this project has identified a "common family tree" of HGSOC from different patients.

**Robert Kurman, M.D., Johns Hopkins University** – A multi-organization collaboration is working to identify and characterize the early changes that lead to HGSOC development. The researchers demonstrated that an early lesion in the fallopian tube, called "serous tubal intraepithelial carcinoma (STIC)" is the precursor of HGSOC, and they developed and validated a publically available algorithm for the diagnosis of STIC.

**Charles Reynolds, M.D., Ph.D., Texas Tech University Health Sciences Center** – In a high-risk/high-reward Pilot award, OCRP researchers are testing Fenretinide (4-HPR), an anticancer drug based on vitamin A, in combination with other anti-cancer drugs, against a patient-derived intraperitoneal ovarian cancer xenograft animal model.



**The OCRP has produced many high-impact advances in the prevention, detection, diagnosis, and treatment of ovarian cancer:**

**Prevention, Detection, and Diagnosis**

- RAD51D Genetic Testing Kit
- OVA1™ Diagnostic Index Test
- Genetic Testing Guidelines for Ovarian Cancer
- A Computational Approach to Diagnosing Precursor Lesions to Ovarian Cancer
- Ovarian Cancer Risk-Reducing Surgery: A Decision-Making Resource

**Treatment**

- Targeting Tumor Vasculature to Eliminate Ovarian Cancer Cells
- Using MSC1 Immunotherapy to Create an Anti-Tumor Response
- Virus-Based Toxin Delivery for Ovarian Cancer Tumors
- Using NSAIDs to Treat Ovarian Cancer

**New Research Tools**

- New Animal Model of Spontaneous Epithelial Ovarian Cancer
- New Model to Study the Effect of BRCA1 on Ovarian Cancer
- New Endometriosis Ovarian Cancer Animal Models
- The Effect of Two Oncogenes on the Development of Ovarian Leiomyosarcoma
- Using Animal Proteins to Predict Ovarian Cancer Risk in Humans
- The Ovarian Cancer Academy: Training Dedicated Researchers

# Parkinson's Research Program

## Program History

Parkinson's disease (PD) is a degenerative movement disorder of the central nervous system 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 appropriation) was initiated in FY97 to provide support for research of exceptional scientific merit leading to an understanding of the cause, prevention, and treatment of 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 FY15, $388.75M has been appropriated by Congress for PD research. The FY16 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.

## Military Relevance

Several risk factors for the development of PD that are of particular interest to the military community have been identified in peer-reviewed studies. The most significant risk factors include exposure to agriculture-type chemicals (including pesticides, insecticides, and solvents); traumatic injury to the head; depression; prolonged physiologic or mental stress; repeated or prolonged disruption of sleep architecture; and repeated or prolonged disruption of autonomic nervous function. These may immediately impact both physical and cognitive performance, as well as predispose Warfighters to neurodegeneration.

## Vision

Slow the progression of, prevent, and cure Parkinson's disease in order to lessen personal and societal impact of the disorder

## Mission

Identify surrogate markers of the disease, correlate distinctive clinical features with specific clusters of these markers, and develop interventions in bimolecular pathways that link markers and expressed clinical features

**Paul Greengard, Ph.D., (pictured) and Lars Brichta, Ph.D.** The

Rockefeller University has identified a protein, SATB-1, that represents the first known abnormality in the death of dopaminergic neurons. Neurotoxic models of PD cause a decrease in the level of SATB-1 associated with the death of dopamine neurons. Genetic depletion of SATB-1 in dopamine neurons also causes death of these cells. The results provide a new avenue for the development of drugs useful for the treatment of PD.

# Program Research through the Years

**Michael Schwarzschild, M.D., Ph.D., Massachusetts General Hospital,** investigates the role of purines, in particular adenosine, caffeine, and urate, in the progression of PD in an effort to develop improved therapeutic strategies. With his epidemiological collaborators, he demonstrated that higher serum urate concentrations are a predictor of slower clinical decline, as well as a lower risk of developing PD. Convergent preclinical evidence from his laboratory demonstrated the neuroprotective effects and mechanisms of urate in animal and cellular models of PD and substantiated the rationale for clinical development of urate-elevating therapy as a candidate disease-modifying strategy in PD. He currently leads a Phase III randomized clinical trial of the urate precursor inosine to investigate its potential to slow disease progression.

**Howard Federoff, M.D., Ph.D., University of California at Irvine,** has focused on developing a therapeutic intervention targeting a new target, PGC-1alpha, that is correlated with the initiation and progression of Parkinsonian neurodegeneration. Preliminary research indicates that reduction in the molecular functions of the protein PGC-1alpha occurs during the initiation and progression of Parkinsonian conditions. Development and validation of PGC-1alpha's altered molecular function in PD may provide a means of preventing disease progression in susceptible populations and/or mitigating the consequences of diminished function in PD patients, offering the possibility of a disease-modifying treatment. Dr. Federoff has applied for a patent covering the use of a candidate compound targeting PGC-1alpha as a potential treatment for PD.

2010

2011

2012

2013

2015

**Judith Potashkin, Ph.D., Rosalind Franklin University of Medicine and Science,** works on the development of diagnostic strategies for PD; specifically, investigating potential biomarkers. Analysis of changes in messenger RNA (mRNA) levels in whole blood led to the identification of hepatocyte nuclear factor (HNF4A) and polypyrimidine tract-binding protein 1 (PTBP1) mRNAs as promising biomarkers of early-stage PD. The same study indicated that both markers may be useful to monitor disease progression, and HNF4A showed promise as a biomarker to monitor disease severity. Identification of these biomarkers contributes to the understanding of the molecular mechanisms of disease and can help track the therapeutic efficacy of potential disease-modifying treatments.

**D. James Surmeier, Ph.D., Northwestern University,** researched effects of calcium entry through L-type channels in dopaminergic neurons of the substantia nigra during pacemaking. Loss of these neurons, thought to be caused by mitochondrial oxidative stress, results in PD. Dr. Surmeier's research revealed that calcium entry through L-type channels elevates mitochondrial oxidant stress. Inhibiting L-type channels reduces mitochondrial stress and increases neuronal resistance to other insults. Epidemiological work shows that use of L-type channel inhibitors is associated with a significant reduction in the risk of developing PD. These studies have led to a 56-center, 5-year Phase III clinical trial to determine whether an FDA-approved L-type channel inhibitor can slow the progression of early stage PD.

**Kenneth Marek, M.D., Institute for Neurodegenerative Disorders**

**"The PARS study is the Parkinson's Associated Risk Syndrome (PARS) study. And that really is focused on trying to identify individuals who might be at risk to develop Parkinson's disease before they have the typical symptoms of Parkinson's disease. This is based on the premise that, for Parkinson's disease, as well as for other neurodegenerative disorders like Alzheimer's disease or Huntington's disease, there is a long period of time when there is degeneration in the brain, but symptoms have not yet arisen. . . . So the PARS study is really an opportunity to understand whether we can develop a population of individuals at risk who we could then take advantage of in clinical studies that might be used to test preventive medicines for Parkinson's disease. . . . The funding that we received for PARS was critical to enable a study to take place, and it really took great foresight from the DoD programs because this really required identification of a novel idea, that is, the idea of identifying individuals prior to the onset of symptoms, and (they) had the follow-through to enable us to continue to follow these individuals for now up to 8 years, which is really remarkable in a research project."**

# Peer Reviewed Alzheimer's Research Program

## Program History

The Peer Reviewed Alzheimer's Research Program (PRARP) (formerly the Militarily Relevant Peer Reviewed Alzheimer's Disease Research Program) was initiated in 2011 to address the long-term consequences of traumatic brain injury (TBI) as they pertain to Alzheimer's disease (AD). Military personnel and other individuals who suffer from TBI face an increased risk for developing several long-term health problems. These conditions include Alzheimer's-like dementia, aggression, memory loss, depression, and symptoms similar to those of other neurological diseases. 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 Burden
- Epidemiology

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

- Genomics/Proteomics
- Mechanisms of Pathogenesis
- Care Interventions and Quality of Life
- Caregiver Support
- Diagnostics and Biomarkers
- Novel Target Identification
- Epidemiological Research

Between FY11 and FY15, the program has administered $63M in funding across 58 awards that are intended to address at least one of the PRARP's overarching challenges. Currently, the PRARP research portfolio is balanced between pathological studies, epidemiology, new diagnostics, and quality of life research.

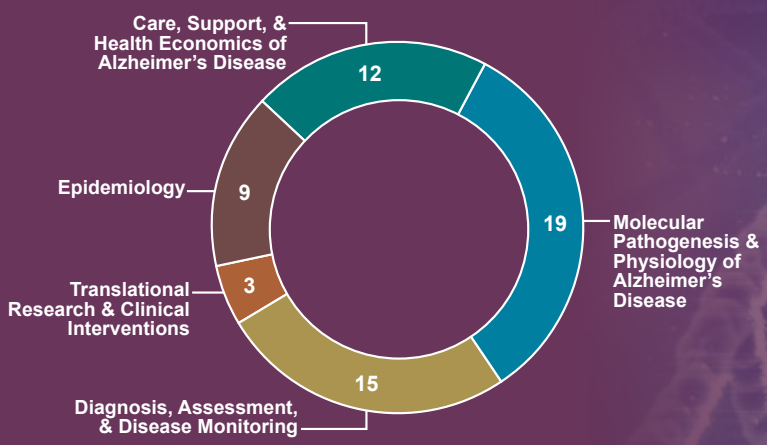
## Vision

To address the long-term consequences of traumatic brain injury as they pertain to Alzheimer's disease and Alzheimer's disease-related dementias (ADRD)

## Mission

The PRARP is devoted to (1) understanding the association between TBI and AD/ADRD; and (2) reducing the burden on affected individuals and caregivers, especially in the military and Veteran communities

### FY11–FY15 PRARP Portfolio by Alzheimer's Disease Research Portfolio Ontology Criteria




## Combined Online Assistance for Caregiver Health (COACH)

Over 8 million Veterans receive informal or unpaid care from a family member or friend. These informal caregivers are essential to the health care system, yet they often lack the necessary support to manage their loved one's complex symptoms, as well as their own stress. Traditional interventions to help caregivers have focused on medications and talk therapy. While these programs have had some success, many caregivers have been unable to participate. This is often because of barriers like limited transportation, lack of respite care, limited time, and distance from the health care center.

With funding provided by the CDMRP, Dr. Kaci Fairchild and her team at the Palo Alto VA and Stanford University School of Medicine have developed an innovative intervention that will overcome these barriers. Two hundred caregivers of Veterans with a TBI or dementia are being recruited into a novel, web-based, physical exercise and caregiver skills training program. Caregivers are provided all necessary equipment to fully implement this intervention in their own homes, including a tablet and exercise equipment. All enrolled caregivers participate in regular physical exercise under the guidance of trained exercise professionals, as well as learn essential skills to help their loved ones, while also managing their own health.

Few studies have examined the effectiveness of a multi-modal intervention such as this, and none to our knowledge has been implemented through mobile tablet-based technology. Given the success of exercise training and caregiver skills training interventions, it is important to determine whether combining these approaches and delivering them through mobile tablet-based technology will increase their efficacy, while improving the accessibility and acceptability of these caregiver interventions.

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**Heather M. Snyder, Ph.D., Senior Director of Medical and Scientific Operations at the Alzheimer's Association**

**"**Ending Alzheimer's and dementia is a global problem that requires global collaboration. The Alzheimer's Association is proud of our collaboration with the PRARP funding program. Together, we need to do everything we can to make sure we have the best minds from every part of the world working toward understanding of these diseases and, ultimately, treatments to stop or slow their progression. The PRARP supports some of these best minds, and we are proud to be a part of the process to help better the lives of individuals - living today and in the future - who are affected by Alzheimer's disease.**"**

**Mara Botonis, Us Against Alzheimer's, Consumer Peer Reviewer**

**"There is already enough to be afraid of, enough to be worried about, enough that has been lost when you are diagnosed or love someone with a TBI. Living with TBI can mean a lot of uncertainty, as a thousand little things that you do or say or think or feel may now be altered for both you and your loved ones. Navigating your 'new normal' may require a bottomless reservoir of strength just to get through each day. On top of that, it's positively terrifying to think of a future that may now include an increased risk of Alzheimer's.**

**I'm incredibly thankful for the extraordinary efforts of the PRARP and their drive to improve the quality of life for persons living with TBI and reduce caregiver burden for the families that love them. The PRARP's work has directly resulted in better days for individuals and families that ultimately have more choices on prevention, treatment, care, and even hope for a cure for Alzheimer's, because we all need one less thing to be fearful of."**

# Peer Reviewed Cancer Research Program

## Program History

The Peer Reviewed Cancer Research Program (PRCRP) began in FY09 with an appropriation of $16M and four topic areas, as directed by the U.S. Congress. Following the inaugural year, Congress responded to the needs of Service Members and their families affected by cancer with the addition of new appropriations for the PRCRP and an expanded list of cancers or research topic areas to fund. Through innovative mechanisms, militarily relevant focus areas, and targeted investment strategies to develop the next generation of cancer researchers, the PRCRP has answered the mandate to fund research that will make a difference for Service Members, their families, and other military beneficiaries.

Members of the military are exposed to hazardous environments due to the nature of their service and deployments and, thus, are at risk for the development of many types of cancers. The Department of Veteran's Affairs has acknowledged certain exposures may increase the cancer risk of Service Members and their families (http://www.publichealth.va.gov/exposures/index.asp, VHA-Directive 2003-34, Attachment B). The FY16 PRCRP directly impacts military welfare by providing research into cancers that may develop due to exposure in various uniquely military environments and continues a long-honored CDMRP tradition of transforming health care and improving the well-being for all military beneficiaries. Since its inception, the PRCRP has focused its vision to improve the quality of life by decreasing the impact of cancer on Service Members, their families, and the American public.

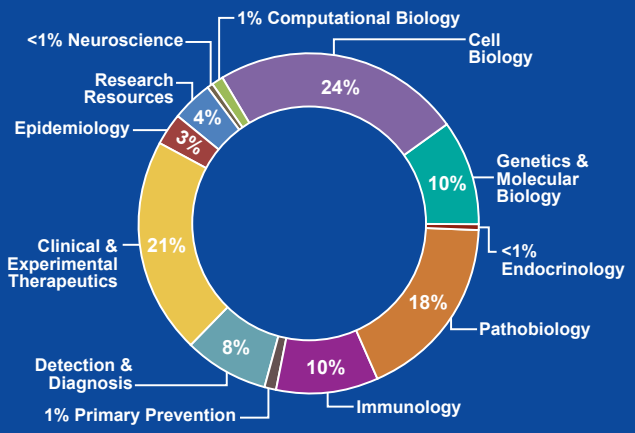
## Vision

To improve quality of life by decreasing the impact 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

### PRCRP FY09–FY15 Research Portfolio Percent Dollars Invested




| Topic Area* | Total Invested FY09–FY15 ($) |
|---|---|
| Blood Cancer | 13.2M |
| Cancers Related to Radiation Exposure | 0.9M |
| Colorectal Cancer | 14.2M |
| Genetic Cancer Research | 12.7M |
| Kidney Cancer | 7.1M |
| Listeria Vaccine for Cancer | 0.8M |
| Liver Cancer | 9.2M |
| Melanoma and Other Skin Cancers | 29.4M |
| Mesothelioma | 7.0M |
| Myleoproliferative Disorders | 2.4M |
| Neuroblastoma | 4.5M |
| Non-invasive Cancer Ablation | 1.8M |
| Pancreatic Cancer | 12.2M |
| Pediatric Cancer | 0.8M |
| Pediatric Brain Tumors | 6.9M |
| Stomach Cancer | 7.7M |

***Each fiscal year, congressional language specifies the topics areas. Not all topics areas have been included in the congressional language each fiscal year. For more information, go to http://cdmrp.army.mil/prcrp/topicareas/topicareas.**

# RESEARCH HIGHLIGHTS

With an FY12 Career Development Award, **Yan Liu, Ph.D.,** from Indiana University in Indianapolis, discovered that loss of necdin enhances leukemia-initiating cell (LIC) proliferation and sensitizes LICs to both chemotherapy and radiotherapy. From this observation, compounds that inhibit necdin may be useful to enhance the efficacy of traditional methods of leukemia treatment.

**Blood Cancer**

Johns Hopkins University's **Seulki Lee, Ph.D.,** awarded an FY13 Career Development Award, characterized a protein expression pattern for irritable bowel disease (IBD)-associated colon cancer in mice and humans. This molecular road map for the transition from IBD to colon cancer will help inform new biomarker testing, as well as treatment strategies.

**Colorectal Cancer**

Funded by an FY14 Idea Award with Special Focus, **David MacPherson, Ph.D.,** from Fred Hutchinson Cancer Research Center, is developing a first-in-class mouse model of bladder cancer. The generation and accessibility of this resource to the greater bladder cancer research community will help provide mechanistic insight and a model for therapeutic interventions.

**Genetic Cancer**

**Maria Czyzyk-Krzeska's, M.D., Ph.D.,** current work at the University of Cincinnati is to define the relationship between tobacco smoke and clear cell renal cell carcinoma with funding from an FY13 Idea Award with Special Focus. She has collected samples from VA patients with and without kidney tumors to analyze the differences in the genetic and signaling landscape due to heavy smoking.

**Kidney Cancer**

**Tyler Curiel, M.D., M.P.H.,** University of Texas Health Science Center at San Antonio, funded by an FY14 Idea Award with Special Focus, is generating *Listeria* and *E. coli* vectors that modify colon epithelial B7-H1 expression, a protein that regulates colon inflammation by preventing microbial imbalance within the gut. From this work, a better understanding of the role of inflammation in colon cancer progression will be elucidated.

**Listeria**

The University of Connecticut's **Kamal Khanna, Ph.D.,** with funding from an FY13 Career Development Award, generated a virus-mediated vaccine that elicits potent, long-lasting tumor resistance. Immunization with this viral vector extends the life of mice with a highly metastatic form of melanoma. The vaccine, in combination with FDA-approved therapies, will be optimized for melanoma treatment.

**Melanoma**

With funding from an FY13 Idea Award with Special Focus, **Arti Shukla, Ph.D.,** University of Vermont, discovered that exosomes (lipid-bound packages of nucleic acids and proteins) released from asbestos-exposed cells have a component that specifically homes to mesothelial cells. Stress plays a role in the makeup of these packages, as exosomes collected from cancer cells undergoing starvation contained different "proteomic signatures." Understanding the significance of these changes will clarify the effect of asbestos-induced mesothelial transformation.

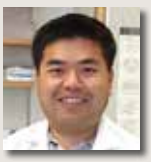
**Mesothelioma**

**Catherine Bollard, M.D.,** (pictured left), Children's Research Institute, and **Eric Yvon, Ph.D.,** MD Anderson Cancer Center, funded by an FY14 Idea Award with Special Focus, are generating a new immunotherapy for neuroblastoma to make cord blood-derived immune cells resistant to inhibitory signals of the tumor microenvironment. Work using this new therapeutic strategy will generate preliminary data in support of clinical trials for neuroblastoma patient treatment.

**Neuroblastoma**

**Sunitha Nagrath, Ph.D.,** of the University of Michigan, developed a microfluidic cell sorter for the detection of circulating tumor cells from blood with the funds from an FY12 Career Development Award. The device brings enhanced specificity, sensitivity, and throughput to the early detection of cancer metastases.

**Pancreatic Cancer**



As an FY12 Visionary Post-doctoral Fellow, **Yujie Huang, Ph.D.,** from Cornell University, identified a cellular marker on bone marrow-derived cells to characterize glioma progression. Transgenic mice lacking this marker protein have delayed glioma tumor progression. Validation of the biomarker signaling during malignant transformation is currently underway.

**Pediatric Brain Tumor/ Cancer**

# Peer Reviewed Medical Research Program

## Program History

Since 1999, the Peer Reviewed Medical Research Program (PRMRP) has supported research under topic areas directed by Congress, with an underlying goal of enhancing the health and well-being of military Service Members, the Veteran population, and their families. Through FY15, Congress has appropriated $1.092B, which has supported 840 research awards. PRMRP has funded research projects in over 120 different congressionally directed topic areas that address a wide range of fields including autoimmune diseases and immunology, cardiovascular health, infectious diseases, internal medicine, neurological and psychological health, orthopedic and regenerative medicine, and respiratory health and injury. The FY16 Congressional appropriation is $278.7M to solicit research projects in 39 topic areas.

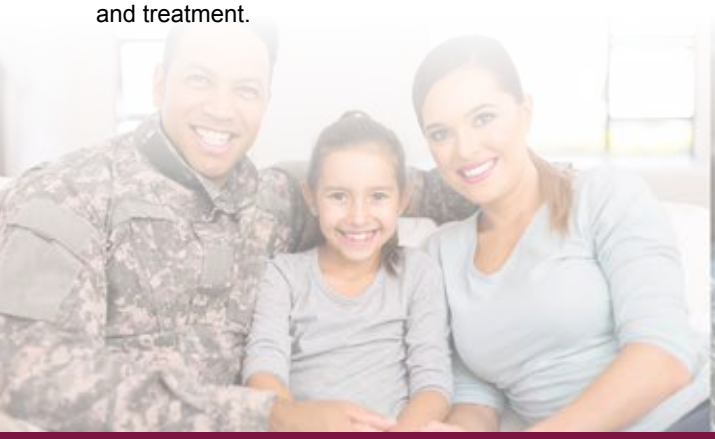
The PRMRP is committed to funding basic, translational, and clinical research including clinical trials that will strongly impact the understanding of disease and injury etiology, as well as the development and implementation of devices, therapies, and clinical guidance that will change the face of prevention, diagnosis, and treatment.

## Vision

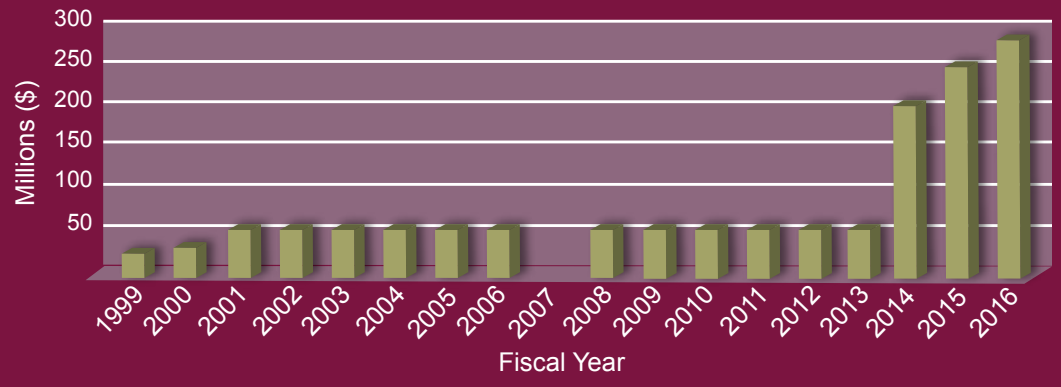
Improve the health and well-being of all military Service Members, Veterans, and beneficiaries

## Mission

Identify and select military health-related research of exceptional scientific merit



### PRMRP Appropriations FY99–FY16

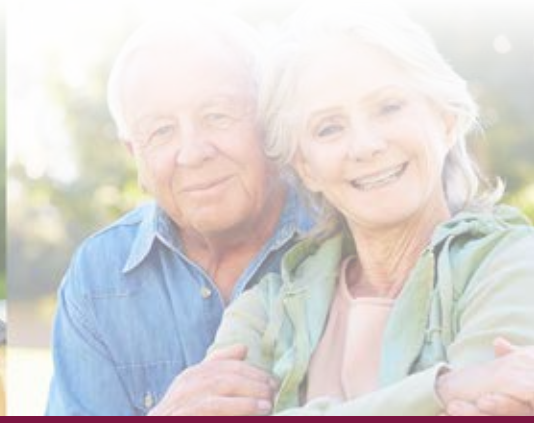


## The PRMRP provides funding opportunities that support original ideas along the entire spectrum of laboratory and clinical research.

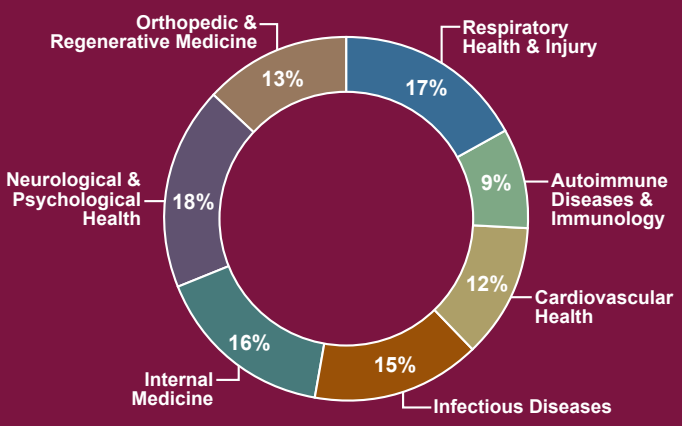
### *FY15 and FY16 PRMRP Funding Opportunities*

**Bench** → **Bedside**

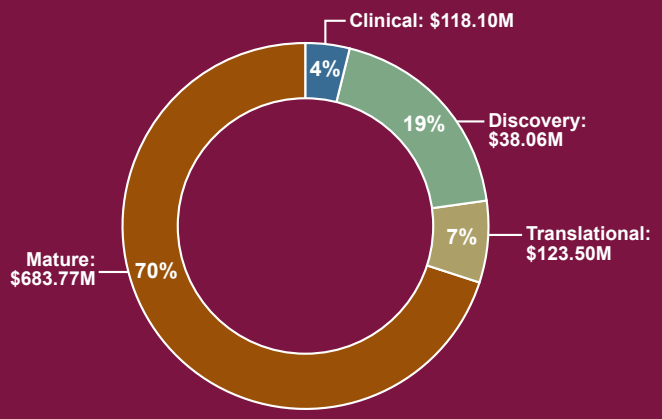
| Discovery | Mature | Translational | Clinical |
|---|---|---|---|
| **Discovery**<br>• Innovative, non-incremental research that will provide new insights, paradigms, technologies, or applications | **Investigator Initiated Research**<br>• Research with the potential to yield highly impactful data that could lead to major advancements<br>**Focused Program**<br>• A set of complementary, synergistic research projects addressing an overarching challenge | **Technology/Therapeutic Development**<br>• Product-driven research that translates promising preclinical findings toward clinical applications | **Clinical Trial**<br>• Evaluation of novel interventions in patient populations |



### FY99–FY15 Portfolio by Research Area




### FY99–FY15 Portfolio by Percent of Awards



**The PRMRP supports research in Congressionally specified topic areas that span across a wide range of health conditions, diseases, and research fields for the benefit of military Service Members, Veterans, military health system beneficiaries, and the American public.**

| Autoimmune Diseases and Immunology | |
|---|---|
| Arthritis | FY15 |
| Food Allergies | FY15 |
| Hereditary Angioedema | FY15 & FY16 |
| Inflammatory Bowel Disease | FY15 & FY16 |
| Lupus | FY15 & FY16 |
| Rheumatoid Arthritis | FY15 & FY16 |
| Scleroderma | FY15 & FY16 |

| Cardiovascular Health | |
|---|---|
| Cardiovascular Health | FY15 |
| Congenital Heart Disease | FY15 & FY16 |
| Diabetes | FY15 & FY16 |
| Vascular Malformations | FY15 & FY16 |
| Women's Heart Disease | FY15 & FY16 |

| Respiratory Health and Injury | |
|---|---|
| Acute Lung Injury | FY15 & FY16 |
| Burn Pit Exposure | FY15 |
| Constrictive Bronchiolitis | FY16 |
| Metals Toxicology | FY15 & FY16 |
| Pulmonary Fibrosis | FY15 & FY16 |
| Respiratory Health | FY15 & FY16 |

| Internal Medicine | |
|---|---|
| Focal Segmental Glomerulosclerosis | FY16 |
| Integrative Medicine | FY15 & FY16 |
| Interstitial Cystitis | FY15 & FY16 |
| Mitochondrial Disease | FY15 & FY16 |
| Non-Opioid Pain Management | FY16 |
| Pancreatitis | FY15 & FY16 |
| Polycystic Kidney Disease | FY15 & FY16 |

| Infectious Diseases | |
|---|---|
| Antimicrobial Resistance | FY16 |
| Dengue | FY15 |
| DNA Vaccine Technology for Postexposure Prophylaxis | FY15 |
| Emerging Infectious Diseases | FY16 |
| Healthcare-acquired Infection Reduction | FY15 |
| Hepatitis B | FY15 & FY16 |
| Influenza | FY15 & FY16 |
| Malaria | FY15 & FY16 |
| Pathogen-Inactivated Dried Plasma | FY15 & FY16 |
| Tuberculosis | FY16 |
| Vaccine Development for Infectious Disease | FY16 |

| Neurological and Psychological Health | |
|---|---|
| Acupuncture | FY15 |
| Chronic Migraine and Post-Traumatic Headache | FY15 & FY16 |
| Dystonia | FY15 & FY16 |
| Fragile X Syndrome | FY15 & FY16 |
| Hydrocephalus | FY15 & FY16 |
| Psychotropic Medications | FY15 & FY16 |
| Rett Syndrome | FY16 |
| Sleep Disorders | FY15 & FY16 |
| Tinnitus | FY15 & FY16 |

| Orthopedic and Regenerative Medicine | |
|---|---|
| Advanced Prosthetics | FY15 |
| Nanomaterials for Bone Regeneration | FY15 & FY16 |
| Osteoarthritis | FY15 |
| Post-Traumatic Osteoarthritis | FY15 & FY16 |

## Springboard for Translation in Military Medicine

**To date, 11 PRMRP-supported projects have been selected for further funding totaling over $37M by the Joint Warfighter Medical Research Program (JWMRP). These projects have been identified as highly relevant to military medical capability gaps, and the JWMRP provides an opportunity to advance the development of each technology toward products that will close those gaps. Examples of PRMRP-initiated efforts receiving support from the JWMRP include:**

- **Investigational New Drug-enabling studies for novel non-narcotic analgesics, radiation countermeasures, biomaterials for bone regrowth, and malaria prophylaxis agents**
- **Preclinical development of novel therapeutics for the prevention of tinnitus**
- **Testing of an enhanced Dengue vaccine**
- **Clinical efficacy of an oral preventative for travelers' diarrhea**
- **A neuroprosthesis for mobility after spinal cord injury**

# PRMRP Supported Advances

## 1999

**Dr. Gregory Belenky** developed an unobtrusive, wrist-worn actigraph with an embedded mathematical performance prediction algorithm for tracking activity and sleep periods.

**Dr. Michael Roy** conducted a clinical trial showing that short-term combination exposure to pyridostigmine, diethyltoluamide, and permethrin bromide, suggested as a cause of Gulf War Illness, does not adversely impact physical or cognitive performance.

## 2001

**Dr. Jeffrey Mason** developed a field-deployable liposome polymerase chain reaction assay to detect botulinum, cholera, and tetanus toxins in environmental and biological specimens.

## 2002

**Dr. Barbara Soller** developed CareGuide™, a portable, fiber-optic, near-infrared spectroscopic sensor system that noninvasively measures muscle pH, oxygen, and hematocrit.

**Dr. Mark Horwitz** developed a novel tularemia vaccine against aerosolized *F. tularensis* bacteria and showed in animal tests that it is less virulent and more efficacious than the available, relatively toxic vaccine.

## 2003

**Dr. Vincent Njar** conducted toxicology and pharmacokinetics testing of next-generation retinoic acid metabolism blocking agents (RAMBAs) and showed the lead candidate is potent against endocrine-sensitive and -resistant breast cancer cells.

## 2005

**Dr. Roy Bloebaum** developed a percutaneous osseointegrated prosthesis that allows direct skeletal attachment of prostheses to amputated limbs and demonstrated load-bearing ability and lack of infection for up to 12 months in an animal above-knee amputation model, leading to an ongoing Phase I clinical trial.

## 2006

**Dr. Laurence Cooper** developed a method, now being evaluated in a first-in-human clinical trial, for genetically modifying T-cells to eradicate malignant B-cells during haploidentical hematopoetic progenitor-cell transplant to treat leukemia and lymphoma, circumventing the need for HLA-identical donors and reducing the risk of graft-versus-host disease.

**Dr. Larry Kwak** optimized a chemokine-idiotype fusion DNA vaccine for treatment of lymphoplasmacytic lymphoma that is now undergoing testing in a Phase I clinical trial.

## 2008

**Dr. Gabriele Gusella** discovered that knocking out expression of the extracellular matrix receptor Integrin beta 1 in a mouse model of autosomal-dominant polycystic kidney disease (ADPKD) prevents renal cystogenosis, identifying Integrin beta 1 as an essential mediator of cyst formation and a potential target for the first therapeutic to treat ADPKD.

**Dr. Wolfgang Fink** adapted a non-invasive visual performance assessment system that measures 3-dimensional visual field defects to be web-based and accessible worldwide, with automated analysis capabilities.

## 2009

**Dr. Curtis Harris** validated a 4-gene prognostic classifier in multiple independent, ethnically and geographically diverse patient cohorts, resulting in a signature that can identify high-risk patients with early-stage lung cancer who may benefit from adjuvant chemotherapy.

**Dr. Michael Hogarty** discovered that targeting neuroblastoma with multiple polyamine-targeting drugs in combination with chemotherapy was more effective at slowing, halting, and preventing disease in animal and in vitro models than single agents, leading to a Phase I clinical trial of two polyamine blockers in combination with chemotherapy agents in children with relapsed neuroblastoma.

## 2010

**Dr. Sharon Shacham** demonstrated that KPT-330, a first-in-class, oral Selective Inhibitor of Nuclear Export drug, can cause growth arrest and apoptosis in neuroblastoma cell lines in vitro and repress tumor growth in a mouse neuroblastoma xenograft model.

**Dr. Kathleen Sweadner** created the first mouse model to exhibit consistent hallmark symptoms of stress-sensitive dystonia, and established two quantitative behavioral tests that will allow for future drug screening and testing using this model.

## 2011

**Dr. Detlev Boison** showed that DNA hypermethylation modulated by adenosine is important for the initiation and progression of epilepsy, and transient, focal delivery of adenosine via silk-based brain implants can reduce DNA hypermethylation and prevent epileptogenesis in an animal model of epilepsy.

**Dr. Michel 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. This therapy is now being evaluated in a clinical trial for treatment of triple-negative breast cancer.

## 2012

**Dr. Xiaonan Han** identified that activation of the signaling molecule STAT5 confers resistance to intestinal injury by increasing intestinal stem cell proliferation and regeneration, identifying it as a potential therapeutic target for fighting diseases such as inflammatory bowel disease that are characterized by persistent enteric infection or inflammation.

**Dr. Jeffrey Borenstein** designed a novel, biodegradable, implantable microdevice capable of delivering drugs to the cochlear for the treatment of tinnitus and other diseases of the inner ear.

# Peer Reviewed Orthopaedic Research Program

## Program History

Orthopaedic injuries represent more than half of all injuries seen in combat and are the largest source of long-term disability in returning Service Members. The impact of these injuries points to an urgent need for orthopaedic research that will provide superior medical care and treatment options for injured Service Members. Blast and other combat-related injuries frequently involve multiple limb traumas to an extent not seen in the civilian setting and are sustained in an environment where access to optimal acute care is limited. Frequent outcomes and complications include amputation, infection, compartment syndrome, heterotopic ossification, and functional muscle loss, among others. The Peer Reviewed Orthopaedic Research Program (PRORP) crafts investment strategies to address these, as well as other 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 $278.5M, toward supporting military-relevant orthopaedic research with the expectation that any research findings will also benefit the general population.

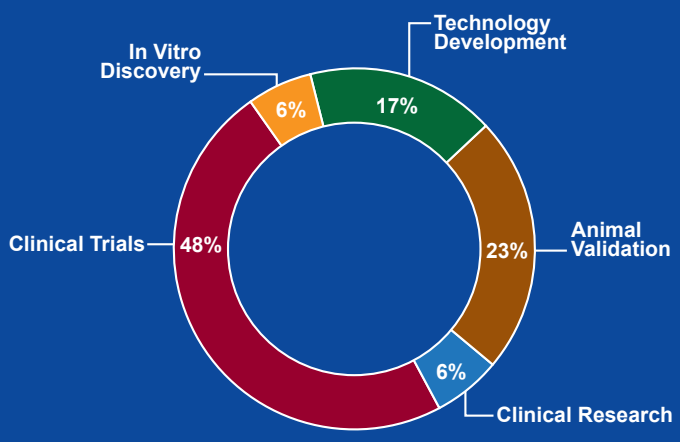
## Vision

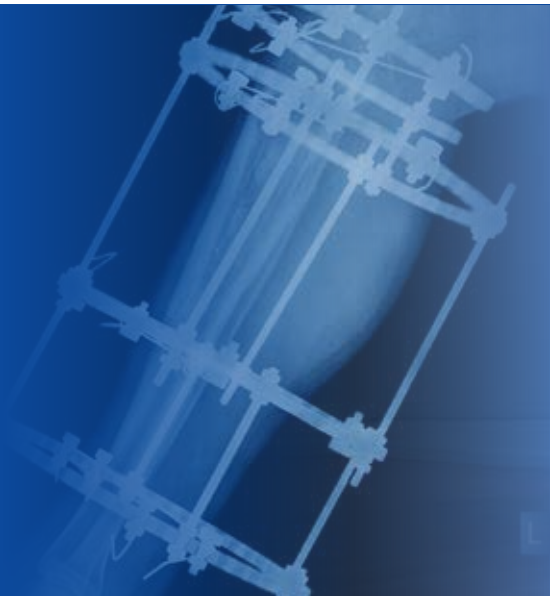
Provide all Warriors affected by orthopaedic injuries sustained in the defense of our Constitution the opportunity for optimal recovery and restoration of function

## Mission

Address the most significant gaps in care for 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

### FY09–FY15 Award Portfolio by Research Type



## Optimizing Techniques for Improving Post-Surgical Bone Defects

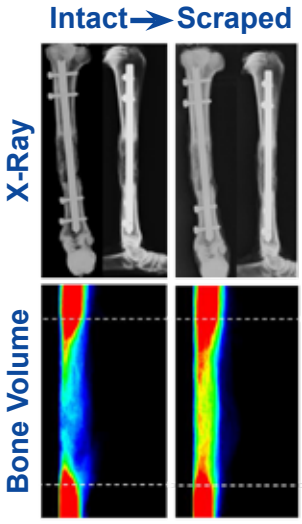
**George Muschler, M.D., Cleveland Clinic Foundation**
**Grace Pluhar, D.V.M., Ph.D., University of Minnesota, Twin Cities**
**Jonathan Forsberg, M.D., Naval Medical Research Center**

High-energy extremity fractures with soft tissue involvement affect thousands of U.S. Service Members and Veterans each year. These fractures require orthopaedic fixation to heal and may involve large regions of bone damage or loss. Treatment of these fractures is also complicated by a high infection rate. The treatment goal for high-energy fractures is a functional limb. The Masquelet technique is a controversial surgical technique that uses an antibiotic-loaded cement spacer to maintain wound space prior to reconstruction and encourages the growth of a biological membrane to promote local bone and tissue healing. It is often debated whether the induced membrane benefits the patient, and whether it should be resected or maintained during reconstruction. In an FY12 PRORP Translational Research Partnership Award,[1] Dr. George Muschler and his colleagues, Dr. Grace Pluhar and Dr. Jonathan Forsberg, explored the benefit of treating segmental bone loss using the Masquelet technique.

The PRORP-funded study used a Chronic Caprine Tibial Defect (CCTD) model in an effort to improve surgical techniques, spacer design, and clinical decision-making. This model employs a stiff metal rod (called an intramedullary nail) to connect and stabilize the two ends of the tibia across a defect. Bone cement is used to induce membrane formation. In a subsequent procedure, the bone cement is removed and replaced with bone graft to promote healing. While the CCTD model started with healthy biology and did not include complications like infection and debridement, the data obtained using the Masquelet technique showed a clear and significant difference in healing rates. Scraping of the inner layer of membrane produced statistically improved bone regrowth in the presence of an antibiotic-loaded spacer. Notably, the mean cross-sectional area of bone produced nearly doubled. These compelling results favor the use of the Masquelet technique in complex surgical reconstruction.

This important study, which is expected to conclude in late 2016, highlights the need for optimizing surgical techniques to improve patient care and prevent complications in high-energy extremity fractures involving bone loss. The results have provided valuable data for surgeons to optimize techniques that improve bone healing and limb salvage. The findings from this study will immediately translate to better clinical care for wounded Warriors, as well as civilians. Additional information on this research can be found on the CDMRP website.[1]

[1] http://cdmrp.army.mil/search.aspx?LOG_NO=OR120082.




***Increased Bone Regeneration When the Inner Aspect of the Induced Membrane is Surgically Scraped Prior to Grafting.***

*Top* – Representative radiographs illustrate that, 3 months after grafting, bone formation roughly doubled in those induced membranes that were scraped prior to grafting with autogenous canellous bone.

*Bottom* – Quantitative MicroCT imaging has been developed to plot the distribution of bone formation around the rod.

**Romney Andersen, M.D.**
**PRORP Programmatic Panel Chair, FY15 and FY16**
**"All members of the PRORP Programmatic Panel are honored to be able to assist wounded Service Members and Veterans through research dedicated to their care."**

# Prostate Cancer Research Program

## Program History

Since its inception in 1997, and over its 19-year history of congressional support totaling nearly $1.5B, the Prostate Cancer Research Program (PCRP) has changed the landscape of biomedical research and energized the prostate cancer (PCa) research community to conduct high-risk research that is decidedly collaborative, innovative, and impactful, ultimately aiming to conquer the disease. The PCRP has made unprecedented inroads in supporting the development of new treatments for advanced PCa, has been the leading supporter of research aimed at understanding and resolving 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 PCa patients.

## Vision

Conquer prostate cancer

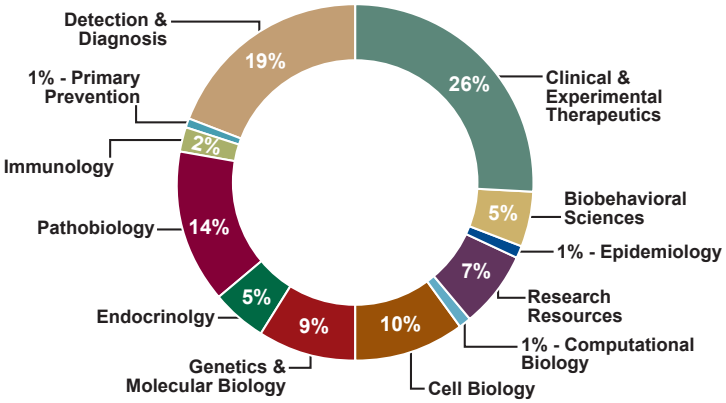
## Mission

Fund research that will lead to the elimination of death from prostate cancer and enhance the well-being of men experiencing the impact of the disease

## Program Portfolio

From 1997–2015, the PCRP funded 3,050 research awards. The supported projects range from exploratory studies that generate cutting-edge ideas to multi-institutional consortia designed to create resources that will transform PCa clinical care. By achieving innovative solutions to critical challenges faced by PCa patients, PCRP-supported researchers can realize the goal of making a direct, positive impact on patients and their families. Since 2009, the PCRP has required that all research funded by the program address the most critical needs of PCa patients, as identified by the PCRP Programmatic Panel. The figure on the right shows the relative numbers of awards the program has supported in these research areas from FY11 through FY15.

### FY11–FY15 PCRP Research Portfolio




**Donald Tindall, Ph.D., Former PCRP Programmatic Panel Member**

**"(Supporting) new investigators is absolutely essential to the progression of our fight on prostate cancer. This is where you get all your new ideas. This is where you have all of your energy. Funding young investigators is absolutely crucial to our development."**

## IMPROVING DETECTION OF EARLY DISEASE...

### Kurt R. Zinn, D.V.M., Ph.D., University of Alabama at Birmingham

Measurement of prostate-specific antigen (PSA) levels in the blood has been a primary method of screening for PCa, but cannot distinguish aggressive vs. indolent cancers. With support from an FY11 Idea Development Award, Dr. Kurt Zinn developed a novel strategy for detecting and monitoring PCa that utilizes the transcription factor protein, Id1 (inhibitor of differentiation-1), which is overexpressed in human prostate tumors and can be directly correlated with Gleason-grade and tumor progression. Exploiting this correlation, Dr. Zinn developed a diagnostic technology that produces two proteins, one for blood-based detection and the other for tumor visualization, in direct proportion to Id1 levels within the prostate tumor cell. This diagnostic vector technology was found to produce signals proportional to Id1 levels and prostate tumor aggressiveness, both in vitro and in vivo, demonstrating its potential to assist clinicians in the detection and treatment of PCa. Moving forward, Dr. Zinn is working on multiple strategies to increase targeted delivery of the agent to tumor cells, thereby advancing the product toward clinical use.

## CLINICAL MANAGEMENT OF ADVANCED DISEASE...

### Peter Nelson, M.D., (pictured left) and Matthias Stephan, M.D., Ph.D., (pictured right) Fred Hutchinson Cancer Research Center

Drs. Peter Nelson and Matthias Stephan of the Fred Hutchinson Cancer Research Center are developing an immunotherapy for use in the treatment of PCa. Using a nanoparticle-based system that can be directly delivered to the patient via injection, they hope to program T cells to express multiple chimeric antigen receptors (CAR) targeting a specific set of PCa antigens. Using CAR T cells capable of recognizing several antigens, rather than only one, could overcome difficulties experienced in current CAR T cell therapies that are limited in their efficacy against phenotypically diverse tumors. This approach also eliminates costly and time-consuming aspects of other T cell therapies that require blood cells to be removed from the patient for programming and proliferation before being reintroduced to the body. Drs. Nelson and Stephan believe that this tailored T cell therapy has the potential to be applicable against a broad spectrum of PCa(s) and provides a flexible platform to adjust therapy for cancers refractive to initial rounds of T cell treatment.

## AND QUALITY OF LIFE FOR PATIENTS

### Ethan Basch, M.D., University of North Carolina at Chapel Hill

**In FY10, the PCRP awarded Dr. Ethan Basch an Idea Development Award to establish standard measurements of pain to provide an endpoint model for clinical trials in PCa, ultimately improving quality of life in patients. By conducting an observational longitudinal study in men with castration-resistant prostate cancer (CRPC) receiving chemotherapy, key pain-related endpoints will be defined, leading to standard design methods in future clinical trials. This clinical trial is currently recruiting patients at four sites. Dr. Basch's experience from this work also resulted in a Cancer paper (2014; 120(5):761-767) that outlines designing strategies for measuring pain palliation and identifying challenges in FDA-reported antitumor therapy clinical protocols spanning almost 20 years. Based on patient-reported outcomes, results showed that improvement in cancer-related pain resulting from antitumor therapy is an important treatment benefit that can support FDA approval of drugs, highlighting the need for improved quality of life in men with CRPC by improving endpoints in PCa clinical trials.**

# Reconstructive Transplant Research Program

## Program History

Since its inception in FY12 through FY16, appropriations totaling $67M have been directed to the Reconstructive Transplant Research Program (RTRP) to advance the science and execution of vascularized composite allotransplantation (VCA) procedures. Many factors related to weaponry, personal protection, and trauma care during Operations Enduring Freedom and Iraqi Freedom resulted in greater survival of those sustaining increasingly severe combat injuries, particularly injuries to the face and the extremities. Repairing such injuries via a donor transplant requires composite tissues, including skin, muscle, bone, fat, nerves, vasculature, and lymph nodes.

In the last three decades, VCA procedures, including approximately 30 face transplants, 20 abdominal wall transplants, and more than 100 upper extremity transplants, have been performed.[1,2] Rates of success are improving, while morbidity and mortality are decreasing, but VCA is still a young science. The intent of the RTRP is to advance the field of VCA to make the procedure possible for a broader population of patients and to restore our Wounded Warriors to duty or to meaningful lives. The RTRP was initiated to fund innovative projects in an array of topic areas within the field of VCA. Beneficiaries of the techniques and technologies developed with this funding include injured Service Members, Veterans, their caregivers, and family members, as well as civilians who have suffered catastrophic tissue loss.

[1] Kueckelhaus M, Fischer S, Seyda M, et al. 2016. Vascularized composite allotransplantation: current standards and novel approaches to prevent acute rejection and chronic allograft deterioration. *Transpl Int* 29(6):655-662.

[2] Broyles JM, Berli J, Tuffaha SH, et al. 2015. Functional abdominal wall reconstruction using an innervated abdominal wall vascularized composite tissue allograft: a cadaveric study and review of the literature. *J Reconstr Microsurg.* 31(1):39-44.

## Vision

Removing the barriers to vascularized composite allotransplantation

## Mission

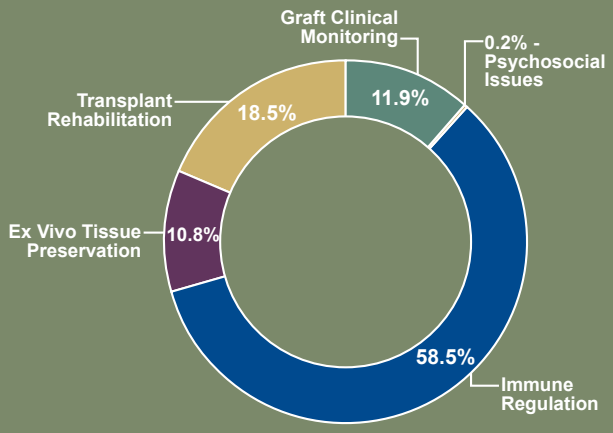
Delivering innovative solutions in the field of vascularized composite allotransplantation to include optimization of patient selection and the restoration of form, function, appearance, and psychosocial health to those who have been catastrophically injured

## RTRP Research Focus

**Each year the RTRP Programmatic Panel reviews the science and funding landscape of the field, as well as the current RTRP investment portfolio, and identifies the most critical gaps and needs for the program. The focus areas and their current representation in the RTRP portfolio are shown below:**

1. **Immune system regulation, as specifically applied to VCA**
2. **Improve ex vivo VCA tissue preservation techniques or technologies to extend the time between procurement and transplantation (goal: 24 hours)**
3. **Reconstructive transplantation rehabilitation**
4. **Graft clinical monitoring - acute and chronic, as applied to VCA**
5. **Psychosocial issues associated with VCA**

## FY12–FY15 Research Portfolio

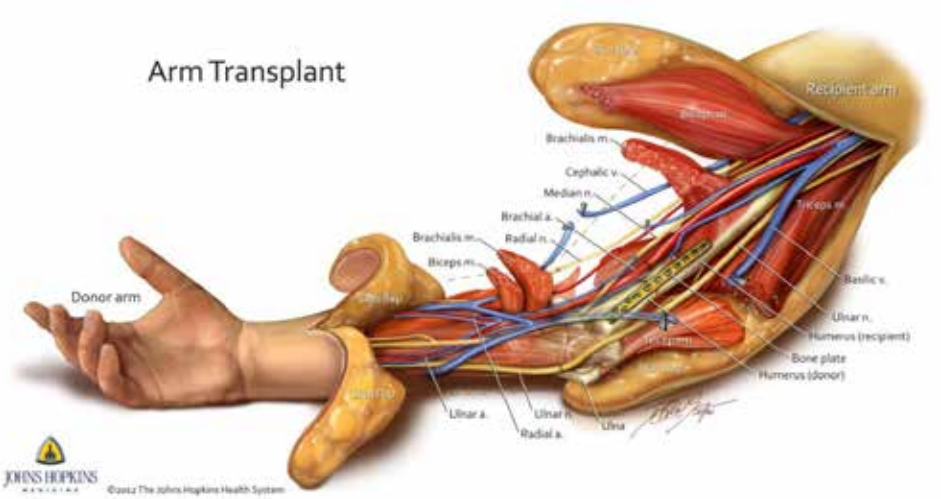



**(% Dollars Invested)**
**Due to rounding, percentages do not add to 100%.**

## Vascular Composite Allotransplantation - Tailored to Fit

As with solid organ transplantation, the VCA transplant team must maintain donor tissue viability and prevent immune-mediated rejection. An additional consideration in VCA is the need to join several different kinds of tissue. Taking a hand/arm transplant as a model, the graphic illustrates the complex logistics. In contrast to the Frankenstein image of a circumferential cut across all layers of tissue, tissue "seams" are offset from each other and designed for each tissue type. Bones are cut at an oblique angle to maximize the surface area at the join and improve osseointegration. Nerve connections are made as distal to the graft as possible to speed reinnervation. During the reattachment of muscles and tendons, joint flexion is varied to maintain appropriate tendon tension. Arteries are joined end to end or end to side to preserve the best muscle blood supply. Once the first artery is repaired, initial revascularization and graft warming begins. After all arteries and veins have been joined, the skin is sutured – use of flaps as illustrated prevents the formation of a scar "bracelet."[3] With so many steps involved in the process, it's no wonder that SGT Marrocco's bilateral hand transplant required a team of 16 Johns Hopkins surgeons and lasted 13 hours.

SGT Brendan Marrocco greets the press a month after hand transplant surgery at Johns Hopkins Hospital. Photos courtesy of the Johns Hopkins Health System.




[3] MacKay BJ, Nacke E, and Posner M. 2014. Hand transplantation--a review. *Bull Hosp Jt Dis* 72(1):76-88.

**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 Department of Veterans Affairs, 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. About his experience as a consumer reviewer 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."**

# Spinal Cord Injury Research Program

## Program History

Spinal cord injuries (SCIs) are serious and complex neurotraumatic wounds affecting military Service Members serving in Iraq and Afghanistan. The Spinal Cord Injury Research Program (SCIRP) was established by Congress in FY09 with a $35M appropriation to support research into regenerating/repairing damaged spinal cords and improving rehabilitation therapies. From FY10–FY15, Congress appropriated an additional $122.85M to continue this research. The SCIRP focuses its funding on projects that have the potential to make a significant impact on improving the function, wellness, and overall quality of life for military Service Members, as well as their caregivers, families, and the American public. The program funds along the continuum of care from interventions for early injury, rehabilitation and readjustment, and secondary health effects of SCI. This investment is distributed across basic, translational, and clinical studies to meet the needs of the SCI community, as shown below for the 141 projects funded between FY09 and FY15.

## Vision

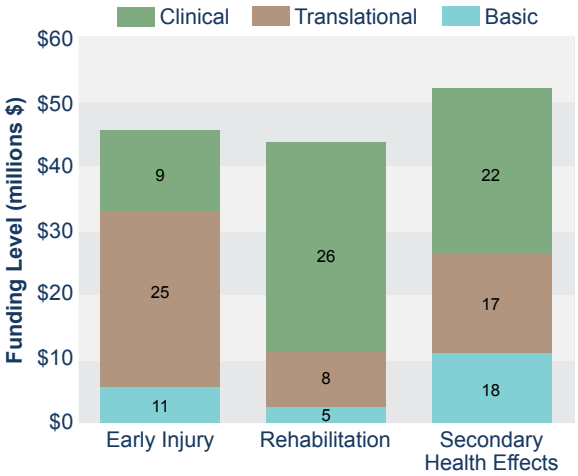
Advance the treatment and management of spinal cord injury and ameliorate its consequences relevant to injured Service Members

## 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

### SCIRP Investment FY09–FY15

Funding is shown in millions of dollars, numbers inside each column are the number of projects. SCIRP has funded 141 projects, corresponding to 163 individual awards.




**Susie Charlifue, Ph.D., Programmatic Panel Member**

**"It has been a professional pleasure to work with military and civilian colleagues on the SCIRP. The program offers a much-needed avenue to fund important research in SCI, addressing the range from pre-clinical studies to clinical trials, to interventions to qualitative research and explorations of issues related to lifetime follow-up of people with SCI and their family members. It is an honor to serve with this group of individuals who are dedicated to improving the lives of people with SCI."**

**Ellen Shackelford, Consumer Peer Reviewer**

**"I am very grateful to have been chosen to serve as a Peer Reviewer for the SCIRP. I think it is a step towards wanting to do what is right for those living with SCI and their families, so everyone can live a life of intention and dignity. I have much hope for those involved in finding a cure and have admiration for all involved in the process."**

## Acute Care

### Noninvasive Optical Monitoring of Spinal Cord Hemodynamics and Oxygenation after Acute Spinal Cord Injury

**Brian Kwon, M.D., Ph.D., University of British Columbia**

Immediately after an SCI, appropriate hemodynamic management is crucial for maintaining spinal cord blood flow and oxygenation and minimizing ischemia. Even small changes can influence long-term neurological outcomes. However, clinicians' ability to monitor and optimize hemodynamic management in acute SCI is hampered by the lack of a real-time measurement tool, as well as insufficient evidence-based research to guide treatment decisions.

Dr. Brian Kwon received an FY15 Translational Research Award to develop an implantable, extradural, near-infrared spectroscopy (NIRS)–based device to provide real-time measurement of spinal cord oxygenation, blood flow, pressure, and metabolism in the injured spinal cord. Dr. Kwon's team will develop the NIRS device using a mini-pig model of acute SCI. If successful, the next step will be development of a device for human use. This project complements earlier work supported by two FY13 awards from the SCIRP to Dr. Kwon on hemodynamics, intraparenchymal spinal cord pressure, spinal cord perfusion, and outcomes in acute SCI.

Taken together, Dr. Kwon's proposed initiatives will accelerate the clinical introduction of new health care technology and have the potential to inform clinical practice guidelines for the management of acute SCI.

## Restoring Function

### Restoring Proprioception via a Cortical Prosthesis: A Novel Learning-Based Approach

**Philip Sabes, Ph.D., University of California at San Francisco**

With support from an FY13 SCIRP Investigator-Initiated Research Award, Dr. Philip Sabes is teaching animals to learn to use artificial proprioception, the feeling of where the body is in space, with the goal of developing a learning-based approach for providing artificial proprioception for SCI patients. People with SCI typically lose their ability to move their limbs and often lose sensation in their limbs as well. Proprioception is one component of that sensation that is particularly important for fluid, effortless, and robust movement control. Dr. Sabes' pilot animal studies are using artificial proprioceptive feedback from a brain machine interface (BMI). BMIs establish direct communication between the brain and artificial actuators, such as robotic limbs or exoskeletons. Dr. Sabes hypothesizes that adding proprioceptive feedback from a prosthetic device will lead to substantially better and more natural BMI control for SCI patients. The successful replication and expansion of these experiments could eventually enable SCI patients to move limbs and/or use assistive devices with accuracy and agility that approach natural levels.

## Rehabilitation and Secondary Health Effects

### A Randomized, Crossover Clinical Trial of Exoskeletal-Assisted Walking to Improve Mobility, Bowel Function, and Cardiometabolic Profiles in Persons with SCI

**Ann M. Spungen, Ed.D., Bronx Veterans Medical Research Foundation, Inc.**

**Physical activity may be dramatically reduced after SCI, leading to many changes, including loss of muscle mass, gain of fat tissue, reduced physical fitness, chronic nerve pain, increased risk of cardiovascular disease, and bladder and bowel dysfunction.**

**Recent advances in exoskeleton technology have made it possible for persons with lower-extremity paralysis to stand and walk upright again. With support from an FY13 Clinical Trial Award, Dr. Ann Spungen and her colleague at the University of Maryland, Dr. Peter Gorman, are testing the hypothesis that, by allowing SCI patients to increase their level of physical activity, exoskeletal-assisted walking devices will lead to favorable changes in metabolism, muscle, and fat and result in a better quality of life.**

# Tick-Borne Disease Research Program

## Program History

The Tick-Borne Disease Research Program (TBDRP) was established in FY16, when the efforts of Lyme disease advocates led to a congressional appropriation of $5M. 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, the yearly cases of Lyme disease and other tick-borne diseases, including spotted fever rickettsiosis, anaplasmosis, and ehrlichiosis, have been increasing steadily for years, currently totaling tens of thousands of people diagnosed annually, with more likely undiagnosed. Globally, the U.S. Military prioritizes tick-borne Crimean-Congo hemorrhagic fever as an operational threat abroad.

Much remains to be determined regarding 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.

## Vision

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

## 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 to improved outcomes

## Program Goals and Strategy

The FY16 TBDRP is seeking research focused in the following areas, with applications addressing persistence and direct detection of Lyme borreliae highly encouraged.

### Pathogenesis:

- Host-pathogen interactions
- Human immune response
- Mechanisms of persistence of Lyme disease
- New research tools to support studies of pathogenesis

### Prevention:

- Interrupting the natural cycle
- Personal protection measures
- Targeted vaccines
- Post-exposure prophylaxis

### Diagnosis:

- Direct detection of tick-borne pathogens or their products in humans
- Biomarkers for diagnosis

### Treatment:

- Innovative approaches to treatment
- Biomarkers of effective prognosis, therapy, and cure
- Basic studies aimed at safe and effective treatments for the cause of persistent symptoms in Lyme disease

The FY16 TBDRP Idea Award funds conceptually innovative, high-risk/potentially high-reward research in the early stages of development that could lead to critical discoveries or major advancements that will accelerate progress in improving outcomes for individuals affected by Lyme disease and other tick-borne illnesses. The Idea Award promotes new ideas that represent innovative approaches to tick-borne disease research and have the potential to make an important contribution to the TBDRP mission.

The FY16 TBDRP Investigator-Initiated Research Award (IIRA) funds highly rigorous, high-impact research with the potential to make an important contribution to the research of Lyme and other tick-borne diseases, patient care, and/or quality of life. The IIRA promotes any phase of research, from basic through translational, including preclinical studies in animal models or human subjects, as well as correlative studies associated with an existing clinical trial to establish proof-of-principle for further development in future studies.

**Pat Smith, Lyme Disease Association**

**"Ticks transmitting Lyme are now found in 50% of counties in the United States. About 18 tick-borne diseases are affecting the U.S. population, transmitted by more than a half dozen ticks whose ranges appear to be spreading, and others are found worldwide, affecting military and civilian populations. Symptoms can range from mild to severely debilitating to causing death, and the diseases are often difficult to diagnose and treat, as one person can have more than one disease at a time. Thus, it is imperative that the Tick-Borne Disease Research Program seeks out novel research projects that will find more sophisticated tests and safe and effective treatment regimens for these globally emerging threats."**

# Trauma Clinical Research Program

## Program History

In FY15, the CDMRP partnered with the U.S. Army Medical Research and Materiel Command's Combat Casualty Care Research Program to begin development of the Linking Investigations in Trauma and Emergency Services (LITES) Request for Proposals (RFP). In FY16, a Congressional appropriation established the Trauma Clinical Research Program to support the LITES initiative. The RFP was released June 2016, and the award was made to Dr. Jason Sperry of the University of Pittsburgh in September 2016.

The RFP supports the creation of a research network of U.S. trauma systems and centers with the capability to conduct prospective, multicenter, injury care and outcomes research of relevance to the DoD. The network will be a platform in which comparative effectiveness studies can be performed on materiel products to assess the feasibility and effectiveness of such products in limited and controlled populations prior to their wider study or operational use. The LITES network may also conduct observational and epidemiological studies to gather preliminary findings for future study and analysis. The information resulting from the LITES network will be integral to informing new and emerging clinical practice guidelines and clinical recommendations, as well as modifying or updating existing standards.

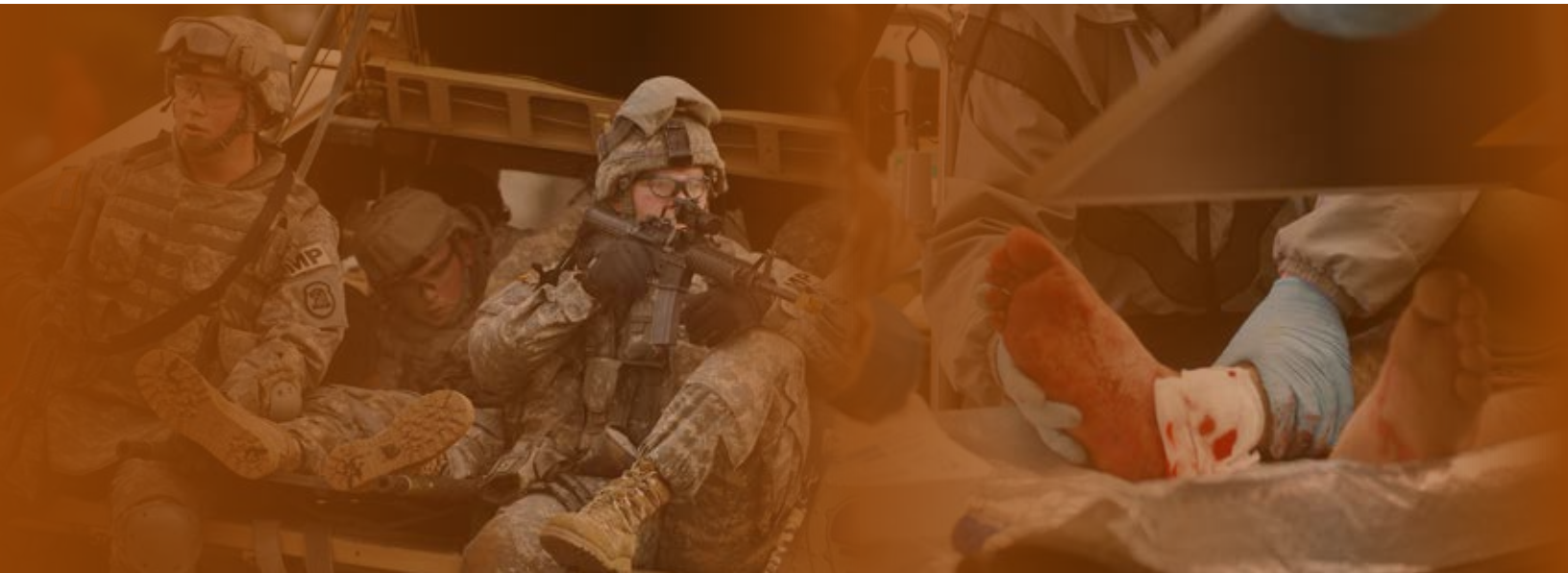
## Vision

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

**The LITES network shall be responsive, flexible, and efficient, to rapidly implement clinical studies that yield operationally oriented, clinically relevant, and timely knowledge in trauma care.**



## LITES Network Overview

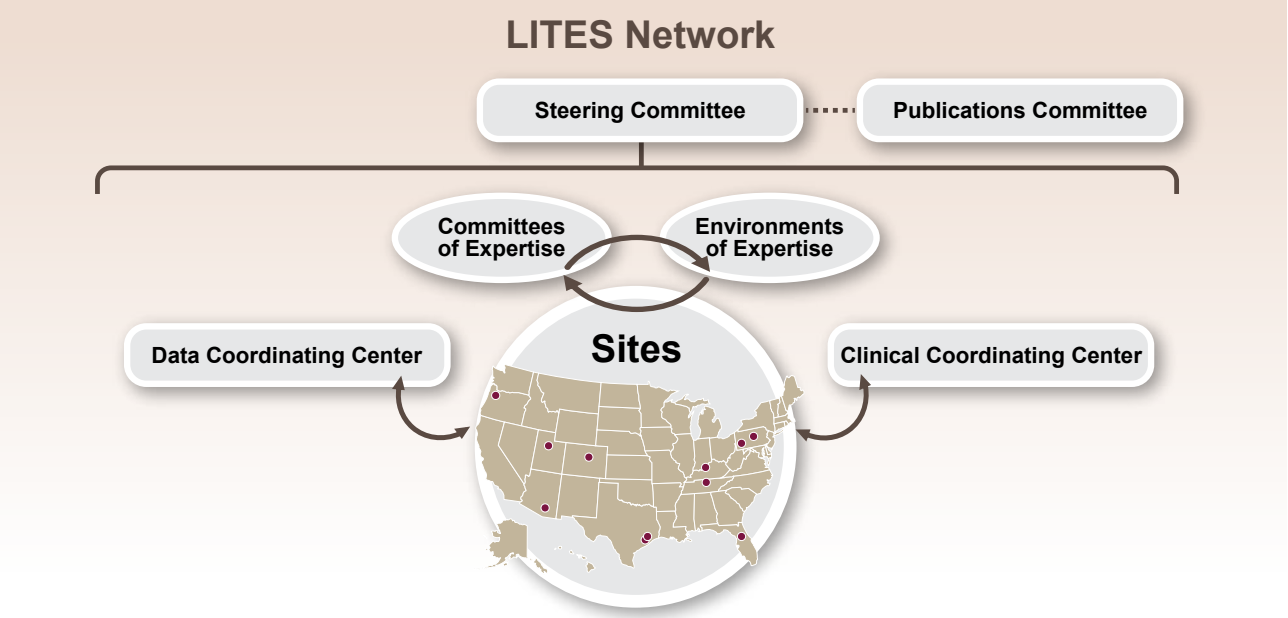
The aim of the inaugural project for the LITES network is to conduct an observational study to understand the epidemiology of traumatic injuries in the network; including regional variations in severity and types of injury, modes and methods of management, and survival and recovery rates (outcomes). This initial foundational study will yield important guidance and create opportunities to improve efficiency for subsequent clinical research to be conducted within the network.

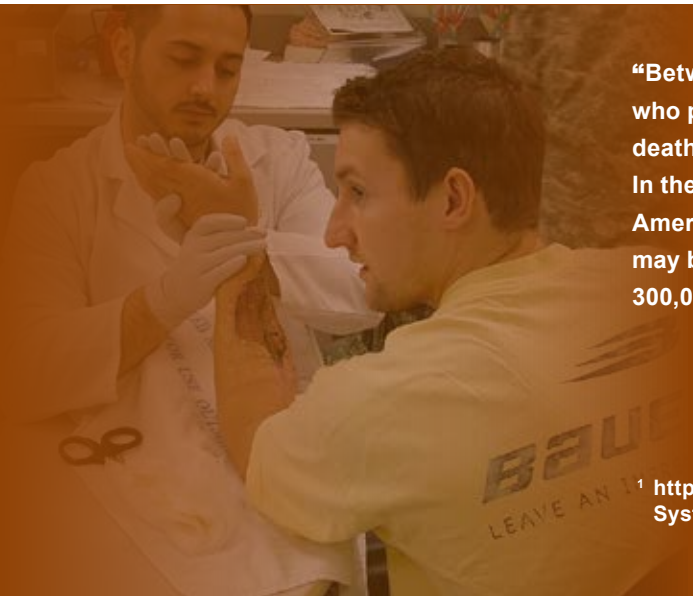
### Key Data to be collected for all trauma patients with an Injury Severity Score ≥ 9:

- Patient demographics
- Pre-hospital data
- Transport data
- Emergency room data
- Operating room data
- Adjunctive treatment and imaging
- Inpatient data
- Use of blood, blood products, and adjunctive blood and coagulation therapies
- Outcome data

### Facility-Level Data (measured at baseline, as well as with any changes occurring during the period of performance):

- Staffing models
- Facility capability
- Available physician specialties
- Clinical practice guidelines used



**"Between 2001 and 2011, approximately 1,000 American Service Members who perished on the battlefield (roughly 25 percent of all battlefield deaths) died of wounds they could potentially have survived. In the civilian sector, where injury is the leading cause of death for Americans under age 46, as many as 1 in 5 deaths from traumatic injuries may be preventable with optimal trauma care, equating to 200,000-300,000 lives that could be saved over the same 10-year period."**

**A National Trauma Care System: Integrating Military and Civilian Trauma Systems to Achieve Zero Preventable Deaths After Injury[1]**

[1] http://www.nationalacademies.org/hmd/Reports/2016/A-National-Trauma-Care-System-Integrating-Military-and-Civilian-Trauma-Systems.aspx

# Tuberous Sclerosis Complex Research Program

## 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 the 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 TSC's relative obscurity. The Tuberous Sclerosis Complex Research Program (TSCRP) was first funded in FY02, when the efforts of TSC advocates led to a congressional appropriation of $1M. Since then, a total of $65M has been appropriated to the program, including $6M in FY16. Today, the TSCRP is one of the leading sources of extramural TSC research funding in the United States.

## Program Portfolio

The TSCRP has funded 128 awards through FY15 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.

## Vision

To lessen the impact of TSC

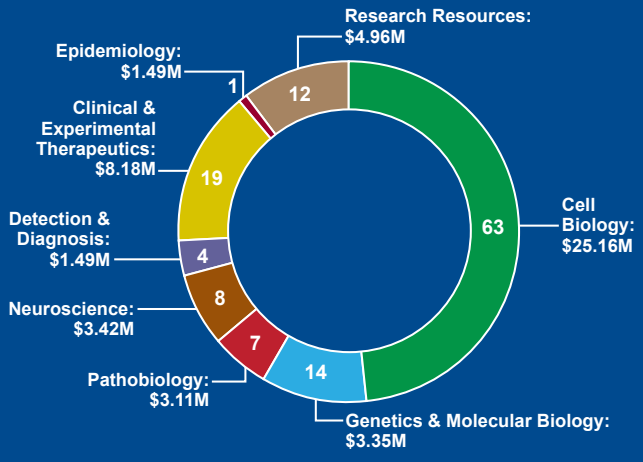
## Mission

To encourage innovative research aimed at understanding the pathogenesis, and preventing and treating the manifestations of TSC

**David Dunn, M.D., Indiana University School of Medicine**
**FY09–FY16 Programmatic Review Panel (FY12–FY14 Chair)**

"The Tuberous Sclerosis Complex Research Program is a valuable resource for researchers and offers real benefits to patients and families. It is an honor to be a part of this excellent program."

### TSCRP FY02–FY15 Research Portfolio




## Inflammation and Epilepsy in TSC

**Michael Wong, M.D., Ph.D., Washington University in St. Louis**

Central nervous system clinical manifestations, such as epilepsy, autism, and cognitive impairment, are very common in TSC and have great impact on both TSC patients and their families, as most people with TSC will have seizures at some point in their lives. Dr. Michael Wong and his team have posited that inflammation may play a role in the development of epilepsy in TSC patients. Several studies have found that proteins indicative of inflammation are present in brain tissue from TSC patients. With an FY11 TSCRP Exploration - Hypothesis Development Award, Dr. Wong and his colleagues screened for markers of inflammation in a mouse model of TSC that develops seizures. They found that specific inflammatory cytokines and chemokines are abnormally activated during epileptogenesis, and treatment with anti-inflammatory drugs specific to these, such as epicatechin-3-gallate, inhibits pathological abnormalities, decreases seizures, and improves survival in a TSC mouse model. Dr. Wong and his team have provided a proof-of-concept preclinical study suggesting that anti-inflammatory treatment could be a potential therapy for epilepsy in TSC patients.

## Novel Inhibitor that May Boost the Effect of mTOR Inhibitors

**Reuben J. Shaw, Ph.D., The Salk Institute for Biological Studies**

TSC is characterized by mutations in the TSC1 or TSC2 gene that cause increased activation of the mammalian target of rapamycin (mTOR) signaling pathway, which leads to abnormal cell growth and tumors. Cells and tumors with hyperactive mTOR signaling have been shown to have a suppressed ULK1 complex and autophagy process, a cellular process that is responsible for the destruction of unnecessary or damaged cellular components. Dr. Reuben J. Shaw received funding from a Fiscal Year 2012 TSCRP Idea Development Award to investigate whether inhibition of ULK1 has therapeutic potential for TSC. Dr. Shaw and his team identified and characterized a small molecule, SBI-0206965, that selectively inhibits ULK1. They were able to show that SBI-0206965 suppresses autophagy induced by mTOR inhibition and prevents ULK1-dependent cell survival following nutrient deprivation by enhancing apoptosis in tumor cells. SBI-0206965 acts as a target inhibitor of ULK1 by converting the growth arrest of cells into a cell death response, which causes the cells to then lose their autophagic maintenance of cell survival. Overall, these results provide early preclinical data to support further development of SBI-0206965 or an analogue for investigation as a therapeutic for TSC.

**Amy Dublinske, FY15 Consumer Peer Reviewer**

**"It has been an honor and a privilege to serve as a consumer peer reviewer for the TSCRP. For over a decade, my family has been battling TSC, which affects our middle daughter, Kierstin. In many ways, TSC has dictated our lives, and I feel that serving on this team has provided the opportunity to not only make a difference for Kierstin, but for the many other families and adults battling TSC on a daily basis as well."**

# Vision Research Program

## Program History

The Vision Research Program (VRP) was created and funded by Congress in FY09 and has awarded 67 grants totaling $49.9M to researchers addressing penetrating eye injuries, corneal healing, retinal/corneal protection, visual dysfunction associated with traumatic brain injury (TBI), the eye blast phenomenon, and vision rehabilitation. (These totals do not include the FY15–FY16 applications recommended for funding [listed below] that are yet to be negotiated and awarded)

- FY09–FY10: 120 pre-applications were received; 50 were invited to submit full proposals, and 12 projects were funded, for a total of $11M.
- FY11–FY12: 151 pre-applications were received; 50 were invited to submit full proposals, and 21 projects were funded, for a total of $13.9M.
- FY13–FY14: 275 pre-applications were received; 151 were invited to submit full proposals, and 34 projects were funded, for a total of $25M.
- FY15–FY16: 99 letters of intent received; 77 applications were submitted for peer review, and 12 applications were recommended for funding, for a total of $18.4M.

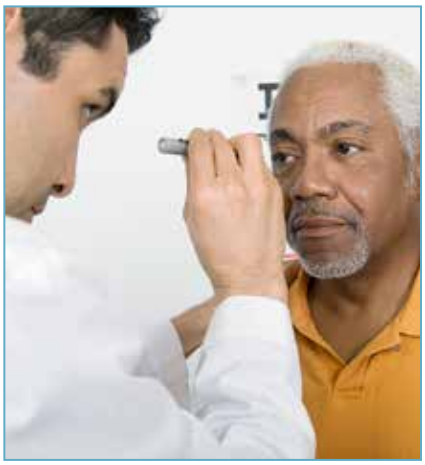
**Vision Capability Gaps:** Epidemiology, mitigation, and treatment of military-relevant injuries and diseases incident to military service to ocular structures and visual system; vision restoration and regeneration; protection and prevention strategies; knowledge, capabilities, and equipment for early responders to diagnose and mitigate military-relevant eye injuries and diseases in austere or remote environments; understanding of pathophysiology of military-relevant injuries and diseases incident to military service; vision and multi-sensory rehabilitation strategies and quality of life measures; understanding of epidemiology, etiology, and treatments of vision and multi-sensory dysfunction associated with TBI; vision readiness standards and assessment strategies; and ocular simulation models and tissue substitutes to replace current tissue-based training and education techniques.

## Vision

Be the model of transformational vision research for our Armed Forces and the nation

## Mission

Improve the care of military personnel affected by eye injuries and diseases by identifying clinical needs and addressing them through directed medical research efforts



## Challenges

**Research to effectively treat acute eye damage can have long-term implications for an individual's vision health, productivity, and quality of life for the remainder of military service and into civilian life. The VRP focuses on the causes, effects, and treatment of eye injury and diseases that, despite their different mechanisms and pathogenesis, all have a common end result: degeneration of the critical components of the eye and impairment or loss of vision.**

## Research Highlights

**Daniel Palanker, Ph.D., of Stanford University** is developing a new prosthetic system to restore sight to individuals with retinal injury or degeneration. Traumatic retinopathy and retinal degeneration causes blindness through loss of photoreceptors, but the inner retinal neurons, which process visual signals and relay them to the brain, often remain well preserved. In Dr. Palanker's system, photovoltaic arrays are implanted under the retina, and each pixel converts light into electrical current that stimulates the inner retinal neurons, thereby introducing information into the patient's visual system. Images from a video camera are processed and projected into the patient's eye by special video goggles, using near-infrared light. This wireless, modular approach is scalable to thousands of pixels and has shown excellent results in preclinical studies. With 70-micrometer pixels, this prosthesis is expected to provide visual acuity close to 20/200, and arrays with even smaller pixels are being developed. This technology is actively being transferred for commercialization and upcoming clinical trials.

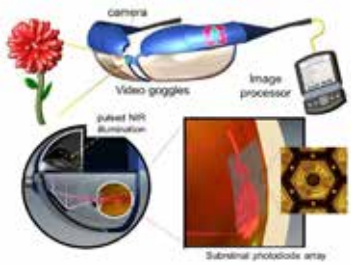



Image captured by the camera is processed and projected from the video goggles onto the sub-retinal prosthesis. Photovoltaic pixels convert pulsed light into pulses of electric current to stimulate the nearby inner retinal neurons.

**Kia Washington, M.D., of the University of Pittsburgh** is working to overcome the obstacles to whole-eye transplantation (WET), a complex surgical procedure that may offer a way to restore sight for individuals with irreversible eye injuries and vision loss. Dr. Washington's team has performed over 100 WET surgeries to date in rats, establishing the first rodent WET model. Prior to Dr. Washington's study, it was not known whether the eye could be viable and maintain its physiologic dynamics after transplantation; her research thus far has proven maintenance of gross morphology, retinal blood flow, aqueous humor dynamics, intraocular pressures, and blood-ocular barriers in transplants. This new model gives the unprecedented ability to collect high-quality data in carefully controlled experiments to bring WET closer to clinical reality.

Ocular blood supply in whole eye transplantation rodent model. (A) Eyeball in transplant graft after heparin perfusion; (B) Eyeball immediately after transplantation and vascular anastomoses; (C) Normal eyeball.

**Barbara Wirostko, M.D., of Jade Therapeutics** (a wholly owned subsidiary of EyeGate Pharmaceuticals, Inc.) is developing a novel ocular bandage using a proprietary cross-linked Hyaluronic Acid polymer to help repair ocular surface injuries. While this proprietary polymer by itself has demonstrated the ability to enhance healing of the ocular surface, based on its intrinsic anti-adhesive and epithelial repair properties, it is also uniquely suited as a locally administered, sustained-release drug delivery system for antibiotics, anti-angiogenics, anabolic proteins, and even limbal stem cells to further enhance ocular healing. Dr. Wirostko envisions this film being applied at the time of injury to help: (1) accelerate the healing and restoration of the ocular surface, (2) Service Members more quickly return to duty, and (3) civilians recover from serious ocular surface disease.

Novel Hyaluronic Acid delivery polymer for repair of ocular injuries.

- **A 2012 study using published data from 2000–2010 estimated that deployment-related eye injuries and blindness have cost the United States $2.3B a year, yielding a total of $25.1B, driven primarily by the present value of long-term benefits, lost wages, and family care.**
- **Traumatic eye injury from penetrating wounds and TBI-related visual disorders ranks second only to hearing loss as the most common injury among "active" military:**
  - **Traumatic eye injuries have accounted for upwards of 16% of all injuries in Operation Enduring Freedom (OEF) and Operation Iraqi Freedom (OIF).**
  - **Eye-injured Soldiers have only a 20% return-to-duty rate, compared to an 80% rate for other battle trauma injuries.**
  - **The Vision Center of Excellence reports 197,000 OEF/OIF Veterans with eye injuries since 2000, and that approximately 75% of all TBI patients experience short- or long-term visual disorders (double vision, light sensitivity, inability to read print, and other cognitive impairments).**

# 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.



# Defense Medical Research and Development Program

## Program History

As directed by the Office of the Assistant Secretary of Defense for Health Affairs (OASD[HA]), the Defense Health Agency, Research and Development (DHA R&D) Directorate manages and executes the Defense Health Program (DHP) Research, Development, Test, and Evaluation appropriation. The USAMRMC CDMRP provides Defense Medical Research and Development Program (DMRDP) execution management support for six DHP core research program areas, including:

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

Joint Program Committees (JPCs), 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 the USAMRMC, operational support responsibilities for the JPCs are provided by multiple execution agents, including the CDMRP, individual laboratories, and advanced developers. In partnership with the JPCs, the CDMRP supports development of program announcements, solicitation and review of applications, full life-cycle management of awards, and program evaluation and planning.

## Mission

To provide full life-cycle operational execution management support for Defense Health Program core research program areas

## Program and Portfolio Areas

From FY10–FY15, the CDMRP has managed 447 DMRDP awards, totaling approximately $530M, to fund basic, translational, and clinical research efforts. 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 are listed on the following DMRDP pages 91-93.

## JPC-1/Medical Simulation and Information Sciences (MSIS)

The JPC-1/MSIS research program plans, coordinates, and oversees a science and technology program focused on improving military medical training and education through medical modeling and simulation systems addressing combat casualty training, medical readiness, health-focused initiatives, and developer tools for medical educators, as well as improving health information sciences through increased interoperability, strategic planning, process development, and medical applications.

JPC-1/MSIS works with the services and joint agencies to address gaps and requirements identified by the Military Health System (MHS) and is responsible for programming research in the following areas:

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

The establishment of JPC-1/MSIS has enabled a more collaborative process to identify and validate the 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 the USAMRMC and the DHA R&D to better align research and development efforts with the needs of the MHS. Additional information about JPC-1/MSIS is available at: *https://mrmc.amedd.army.mil/index.cfm?pageid=medical_r_and_d.msis.overview.*

### *Recent JPC-1/MSIS DHP Research:*

- Applied Cognitive Models of Behavior and Error Patterns; *Christopher Meinberg, Soar Technology, Inc.*
- An Adaptive Tutor for Improving Visual Diagnosis; *Martin Pusic, New York University School of Medicine*
- Medical Cloud Connectivity for Combat Casualty Care; *Gary Gilbert, Telemedicine and Advanced Technology Research Center*

### *Affiliated Research Programs:*

- Joint Warfighter Medical Research Program

## JPC-2/Military Infectious Diseases Research Program (MIDRP)

The JPC-2/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. JPC-2/MIDRP's DHA-aligned mission is focused on the following research portfolio area:

- Polytrauma and Blast Injury

JPC-2/MIDRP's DHP core research program-aligned projects are primarily within the portfolio task areas of Wound Infection Prevention and Management and Antimicrobial Countermeasures. Supported research efforts are focused on development of host immune response and pathogen biomarkers associated with wound infection to inform clinical decisions; development of tools for early detection of drug-resistant organisms; identification of nosocomial pathogens; characterization of antimicrobial resistance patterns; and development of novel and innovative delivery technologies to treat wound infections. This research also emphasizes treatment, with research involving identification of druggable targets against wound infection pathogens and biofilm processes; transition of new candidate therapeutics to preclinical testing; and advancement of promising early leads to first-in-human clinical trials. Additional information about JPC-2/MIDRP is available at: *https://midrp.amedd.army.mil/.*

### *Recent JPC-2/MIDRP DHP Research:*

- Evaluation of Novel Antimicrobial Peptides as Topical Anti-Infectives with Broad-Spectrum Activity Against Combat-Related Bacterial and Fungal Wound Infections; *Louis Edward Clemens, Riptide Bioscience, Inc.*
- Development and Preclinical Evaluation of VT-1598, a Broad-Spectrum and Safe Antifungal to Prevent Fungal (Mold) Infections of Battlefield Wounds; *Edward Garvey, Viamet Pharmaceuticals, Inc.*
- Preclinical Development of an Antimicrobial Nanoemulsion to IND for Multidrug-Resistant Wound Infections; *Suhe Wang, University of Michigan*

### *Affiliated Research Programs:*

- Joint Warfighter Medical Research Program
- Peer Reviewed Medical Research Program
- Tick-Borne Disease Research Program

## JPC-5/Military Operational Medicine Research Program (MOMRP)

The JPC-5/MOMRP seeks to develop effective countermeasures against stressors and to maximize health, performance, and well-being. JPC-5/MOMRP conducts biomedical research to deliver products and solutions to the Warrior that address health and fitness throughout the deployment cycle. JPC-5/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 JPC-5/MOMRP can be found at *https://momrp.amedd.army.mil/.*

### *Recent JPC-5/MOMRP DHP Research:*

- Primary Blast Injury Critiera for Animal/Human TBI Models using Field Validated Shock Tubes, *Dr. Namas Chandra, New Jersey Institute of Technology*
- Evaluation of the Physiological Challenges in Extreme Environments: Implications for Enhanced Training, Operational Performance and Sex-Specific Responses, *Dr. Brent Ruby, University of Montana*

### *Affiliated Research Programs:*

- Alcohol and Substance Abuse Disorders Research Program
- Gulf War Illness Research Program
- Joint Warfighter Medical Research Program
- Peer Reviewed Medical Research Program
- Psychological Health and Traumatic Brain Injury Research Program

## JPC-6/Combat Casualty Care Research Program (CCCRP)

The JPC-6/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. JPC-6/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 JPC-6/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. JPC-6/CCCRP supports the complete range of research activities needed to achieve its goals, from foundational science to improvements in health care services and delivery. Additional information about JPC-6/CCCRP can be found at *https://ccc.amedd.army.mil.*

### *Recent JPC-6/CCCRP DHP Research:*

- Economic Impact of Combat-Related Injuries From the Wars in Iraq and Afghanistan; Ted Miller, Pacific Institute for Research and Evaluation
- Trauma Outcomes and UroGenital Health in OEF/OIF (TOUGH) - A Retrospective Cohort Study with Long-Term Follow-up; *Bradley Pollock, University of California, Davis*
- The Effects of Hypobaria and Vibration Associated With Aeromedical Evacuation on Neurotrauma and Lung Injury in a Rat Blast Model; *Richard McCarron, Naval Medical Research Center*

### *Affiliated Research Programs:*

- Epilepsy Research Program
- Joint Warfighter Medical Research Program
- Military Burn Research Program
- Peer Reviewed Medical Research Program
- Peer Reviewed Orthopaedic Research Program
- Psychological Health and Traumatic Brain Injury Research Program
- Spinal Cord Injury Research Program
- Trauma Clinical Research Program

## JPC-7/Radiation Health Effects Research Program (RHERP)

The JPC-7/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 the JPC-7/ RHERP is focused on the following key area:

- Biomedical Technology for Radiation Countermeasures

### *Recent JPC-7/REHRP DHP Research:*

- Entolimod: A Medical Countermeasure to Reduce the Risk of Death Following Radiation Exposure, *Langdon Miller, Cleveland BioLabs, Inc.*
- Minimally Invasive Radiation Biodosimetry and Evaluation of Organ Responses, *Naduparambil Jacob, Ohio State University*
- Long-Term Followup of the Delayed Effects of Acute Radiation Exposure in Primates, *J. Mark Cline, Wake Forest University Health Sciences*

### *Affiliated Research Programs:*

- Joint Warfighter Medical Research Program
- Peer Reviewed Cancer Research Program
- Peer Reviewed Medical Research Program

## JPC-8/Clinical and Rehabilitative Medicine Research Program (CRMRP)

The JPC-8/CRMRP is focused on definitive and rehabilitative care innovations required to reset injured Service Members in terms of duty, performance, and quality of life. JPC-8/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 JPC-8/CRMRP is focused on the following key areas:

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

JPC-8/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 program has multiple initiatives to achieve its goals, including improving prosthetic function; enhancing self-regenerative capacity; improving limb/organ transplant success; creating full-functioning limbs/organs; repairing damaged eyes; treating visual dysfunction following injury; improving pain management; and enhancing rehabilitative care. Additional information about JPC-8/CRMRP can be found at: *https://crmrp.amedd.army.mil/.*

### *Recent JPC-8/CRMRP DHP Research:*

- Flexible Regenerative Nanoelectronics for Advanced Peripheral Neural Interfaces, *Aaron Baker, University of Texas at Austin*
- Combining Clinically Available Rehabilitative and Regenerative Strategies to Improve Functional Outcomes after Severe Extremity Trauma, *University of Texas at Austin, University of Pennsylvania, Benjamin Corona, U.S. Army Institute of Surgical Research*
- Tissue Engineering Strategies to Maintain Distal Target Efficacy and Promote Full Functional Recovery Following Major Peripheral Nerve Injury, *U.S. Army Institute of Surgical Research, Daniel Cullen, University of Pennsylvania*

### *Affiliated Research Programs:*

- Joint Warfighter Medical Research Program
- Orthotics and Prosthetics Outcomes Research Program
- Peer Reviewed Medical Research Program
- Peer Reviewed Orthopaedic Research Program
- Psychological Health and Traumatic Brain Injury Research Program
- Reconstructive Transplant Research Program
- Spinal Cord Injury Research Program
- Vision Research Program

# Psychological Health and Traumatic Brain Injury Research Program

## Program History

The Psychological Health and Traumatic Brain Injury Research Program (PH/TBIRP) was established by Congress in FY07 in response to the devastating impact of traumatic brain injury (TBI) and psychological health (PH) issues, including post-traumatic stress disorder (PTSD), on our deployed Service Members in Iraq and Afghanistan. Appropriations totaling $300M, $150M each for TBI and PH (including PTSD), were assigned to the CDMRP for the purpose of soliciting and managing critical TBI- and PH-related research and development efforts to benefit Service Members, Veterans, and other beneficiaries of the Military Health System.

## 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

Additional congressional appropriations for the PH/TBIRP were assigned to the USAMRMC between FY09 and FY15, and a modified execution model was established in which strategic oversight is provided by USAMRMC-based research program areas aligned with the Office of the Assistant Secretary of Defense for Health Affairs (OASD[HA]). As directed by the OASD(HA), the Defense Health Agency, Research and Development (DHA R&D) Directorate manages and executes the Defense Health Program (DHP) Research, Development, Test, and Evaluation appropriation, which includes the PH/TBIRP. The DHA R&D Directorate leverages PH/TBIRP funding to support ongoing research and development in three core DHP research program areas assigned to study PH and TBI, including:

- Joint Program Committees (JPC-5)/Military Operational Medicine Research Program (JPC-5/MOMRP)
- (JPC-6)/Combat Casualty Care Research Program (JPC-6/CCCRP)
- (JPC-8)/Clinical and Rehabilitative Medicine Research Program (JPC-8/CRMRP)

These JPCs provide recommendations to the DHA R&D Directorate on research gaps, focus areas, and funding options for the PH/TBIRP. The CDMRP works in partnership with the JPCs to provide operational execution management support as needed for the PH/TBIRP, including development of program announcements, solicitation and review of applications, full life-cycle management of awards, and program evaluation and planning. The CDMRP-managed application review for

**Through FY15, the CDMRP has managed 485 PH/TBIRP awards, totaling over $800M 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 the PH/TBI Supported Initiatives can be found at:**

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

the PH/TBIRP follows a two-tiered model, where consumer involvement continues to be a hallmark. Our nation's Wounded Warriors serve in this capacity for the PH/TBIRP, representing fellow Service Members and Veterans to help identify the most relevant and impactful research. The modified execution process allows greater flexibility for aligning PH/TBIRP congressional special interest funds to complement core DoD research and development efforts. For more information on this execution model, see page 90 (DMRDP Execution).

## PH/TBIRP Recent Research Focus

Research supported by the DoD 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.

### JPC-5/MOMRP

- ***RNA Expression in PTSD in Induced Human Neurons and Blood Cells in Basal and Glucocorticoid-Stimulated Conditions***, *Rachel Yehuda, Ph.D., Icahn School of Medicine at Mount Sinai*
- ***Intranasal Neuropeptide Y for PTSD and Other Stress Triggered Neuropsychiatric Disorders***, *Esther Sabban, Ph.D., New York Medical College*
- ***Consortium to Alleviate PTSD: Treatment of Comorbid Sleep Disorders and PTSD***, *Daniel Taylor, Ph.D., University of North Texas*

### JPC-6/CCCRP

- ***Preclinical Evaluation of FDA Approved Human Neural Stem Cell Engraftment in a Rat Model of Severe Traumatic Brain Injury***; *Ross Bullock M.D., Ph.D., University of Miami*
- ***Development and Validation of Spreading Depolarization Monitoring for TBI Management***; *Jed Hartings Ph.D. University of Cincinnati*
- ***Acute Mild Traumatic Brain Injury Study in a Military (and Civilian) Population Using Advanced Microstructure Imaging in Novel Ultra-High Performance MRI System***; *Thomas Foo, General Electric Company*

### JPC-8/CRMRP

- ***Utility of MRS Brain Biomarkers of Pain Phenotypes after TBI***, *Eva Widerstrom-Noga, Ph.D., University of Miami, Coral Gables*
- ***Preventing and Repairing Combat-Related Proliferative Vitreoretinopathy: Using 3D Engineered Eye Tissue Derived from Human-Induced Pluripotent Stem Cells***, *Kapil Bharti, Ph.D., National Eye Institute*
- ***Effectiveness of a Vestibular Ocular Motor Screening (VOMS) Tool for Identifying mTBI and Tracking Recovery in Military Personnel***, *Anthony Kontos, Ph.D., University of Pittsburgh*

# Small Business Innovation Research and Small Business Technology Transfer Programs

## Program History

The Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) Programs are competitive funding opportunities that are designed to strengthen the role of innovative small businesses in federally funded research and development. Initiated by the establishment of the SBIR program in 1982 by Congress, the goal of the programs is to provide small businesses with critical startup and development support that will allow them to compete successfully with larger businesses and commercialize products while fulfilling government needs. Congress established the STTR program, which requires that small businesses work with nonprofit research institutions, in 1992, with a primary objective of bridging the gap between basic science and commercialization of its innovative discoveries. The programs are organized in three phases of development: Phase I establishes proof of principle; Phase II involves prototype development and testing; and Phase III centers on commercialization. SBIR/STTR funding is available for Phase I and Phase II projects, while Phase III support must come from private and non-SBIR government sources. Eleven federal agencies participate in the SBIR program; five participate in the STTR program, including the DoD. The CDMRP has worked with these programs since FY00 and FY04, respectively, to fill gaps and leverage research and product development not supported elsewhere in the CDMRP portfolio. Since that time, the CDMRP has managed more than 70 Phase I contracts and over 40 follow-on Phase II contracts, totaling more than $70M for areas such as cancer; traumatic brain injury (TBI); wound healing; tissue regeneration; antimicrobials for multidrug resistant bacteria; medical devices; medial simulation, etc. The following page describes a few of the products and research outcomes that have resulted from this funding.

## Program Objectives

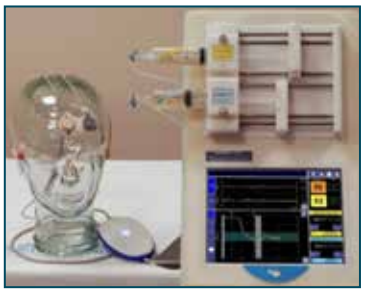
- Stimulate technological innovation
- Increase private sector commercialization of federal research and development
- Increase small business participation in federally funded research and development
- Foster participation by minority and disadvantaged firms in technological innovation

### Cell-Seeded Implant for Guided Lymphatic Regeneration (BioBridge™)

**Secondary lymphedema is a serious, progressive, and global disease that currently has no cure. In the United States and other western countries, it most commonly occurs as a delayed result of cancer treatment, impacting an estimated 25% of breast cancer patients. Fibralign received SBIR Phase I and Phase II funding to develop a much-needed treatment for this disease. In collaboration with Stanford University, a novel therapeutic medical device based on Fibralign's patented Nanoweave™ technology was developed and successfully tested in a translational large animal study. The project builds on over 2 years of collaboration between Fibralign and Stanford resulting in BioBridge™, a thread-like scaffold with a precise nanostructure designed to promote and support regeneration of lymphatic vessels and restore lymphatic function. BioBridge™ is composed of highly purified collagen made to be safely absorbed in the body after completing its task. BioBridge™ was tested in both**

## Deployable Closed-Loop Anesthesia System (AutoTIVA)

NeuroWave Systems was awarded SBIR Phase I and Phase II funding to develop a new computerized anesthesia delivery platform (AutoTIVA) to better support the work of anesthesiologists in combat surgical hospitals and at higher echelons of care. Total Intravenous Anesthesia (TIVA) is an anesthesia regimen where only intravenous drugs are used to achieve and maintain anesthesia during surgery. However, TIVA is not commonly practiced by anesthesiologists due to the lack of supporting technologies to aid in its delivery. The AutoTIVA measures noninvasively and in real time the effect of anesthesia directly at the level of the patient's brain. It then automatically adjusts the delivery rate of the anesthesia drugs every second in order to drive and maintain the patient at the anesthetic depth targeted by the anesthesiologist. Its automation capability makes it also particularly well suited for mass casualty situations and prolonged field care.



The latest rendition features a system that integrates the user interface, brain monitor, and infusion pumps in a single device. Following public disclosures and demonstrations of the AutoTIVA prototype, the Office of Naval Research reached out to NeuroWave and contracted the company to adapt the technology for automated sedation delivery during tactical en-route care. Proprietary infusion pumps have been developed specifically for the US Navy and will be integrated in the AutoTIVA platform in the near future.

## Cognitive/Motor Therapy Application Using Console-Based Videogame Platform (Treasure of Bell Island)


While most people with mild TBI (mTBI) fully recover, 5–15 percent report cognitive symptoms after 1 year post-injury. Blue Marble Rehab, Inc., was awarded SBIR Phase I and Phase II funding to develop a mobile, internet-enabled, digitized and gamified, evidence-based cognitive assessment and training tool, called "Treasure of Bell Island," to evaluate and treat cognitive-perceptual-motor impairments secondary to mTBI. The objectives are to (1) revise the software based on results of the previous pilot study; (2) expand software features to address a greater range of cognitive impairments; (3) expand the database capabilities, and (4) evaluate feasibility, usability, and effectiveness. The assessment battery contains 16 evidence-based standard assessments with over 140 metrics of cognitive function, including attention, memory, executive function, visual processing, and perceptual motor domains. The training tool provides over 60 hours of gameful cognitive practice and captures 75+ metrics of cognitive function across similar domains. Data captured from the cognitive assessment and training tool is stored on secure servers. A web-based dashboard provides end-users, clinicians, and administrators with data from the assessment and training tool that can be used to measure outcomes, track change over time, improve access to care, increase client engagement, and improve client satisfaction.

**small and large animal models and has been shown to support and promote the formation of new lymphatic vessels (lymphangiogenesis). A translational large animal study of lymphedema surgical intervention was successfully conducted jointly with Fibralign, Stanford University, and Hannover Medical School (Germany) and demonstrated the therapeutic efficacy and safety of BioBridge™. This landmark six-month study showed definitively that implanted BioBridge™ supported new lymphatic vessel formation and restoration of lymphatic function. Fibralign has also advanced its technology for fabricating BioBridge™ and completed product development activities to support a successful 510(k) submission. BioBridge™ received 510(k) clearance from the FDA for soft tissue support and repair in January 2016. Using the data from the large animal study and feedback gathered from leading clinicians and surgeons in this field, novel approaches using BioBridge™ are proposed for both treating and preventing this disease. Fibralign initiated a small pilot study in the Dominican Republic at the end of last year and obtained encouraging results. Stanford University is preparing to lead a larger, double-blinded clinical study for patients with breast cancer-related lymphedema and has recently received Institutional Review Board approval and begun enrollment. SBIR funding from the DoD was critical in advancing this important work.**

# Appendix A: FY92–FY15

**Table A-1.** Overview of Appropriations, Applications Received, and Awards Made for FY92–FY15

| Programs Managed by CDMRP | Fiscal Year | Appropriations Received (in millions) | Applications Received | Applications Funded[1] |
|---|---|---|---|---|
| Alcohol and Substance Abuse Disorders | 2014-2015 | $8.0 | 6 | 5 |
| Amyotrophic Lateral Sclerosis | 2007, 2009-2015 | $54.4 | 400 | 45 |
| Autism | 2007-2015 | $59.4 | 1,194 | 131 |
| Bone Marrow Failure | 2008-2015 | $26.6 | 409 | 56 |
| Breast Cancer | 1992-2015 | $3,141.3 | 52,596 | 6,592 |
| Breast Cancer Research Semipostal[2] | 1999-2015 | $24.2 | n/a | 49 |
| Chronic Myelogenous Leukemia | 2002-2006 | $22.1 | 252 | 61 |
| Defense Women's Health | 1995 | $40.0 | 559 | 69 |
| Deployment Related Medical | 2008-2013 | $101.9 | 1,094 | 58 |
| DoD/VA | 1999-2000 | $6.8 | 88 | 9 |
| Duchenne Muscular Dystrophy | 2011-2015 | $16.8 | 100 | 21 |
| Epilepsy | 2015 | $7.5 | 25 | 5 |
| Genetic Studies of Food Allergies | 2009-2010 | $4.4 | 60 | 9 |
| Gulf War Illness | 2006, 2008-2015 | $109.0 | 400 | 125 |
| Institutionally Based Programs | 1995-2010 | $486.3 | 306 | 501 |
| Joint Warfighter Medical | 2012-2015 | $154.0 | 111 | 54 |
| Lung Cancer | 2009-2015 | $89.5 | 2,281 | 166 |
| Military Burn | 2014-2015 | $16.0 | 40 | 27 |
| Multiple Sclerosis | 2009-2015 | $33.1 | 604 | 72 |
| Myeloproliferative Disorders | 2004 | $4.3 | 18 | 9 |
| National Prion | 2002 | $42.5 | 136 | 38 |
| Neurofibromatosis | 1996-2015 | $287.9 | 1,439 | 353 |
| Orthotics and Prosthetics Outcomes | 2014-2015 | $20.0 | 116 | 18 |
| Osteoporosis | 1995 | $5.0 | 105 | 5 |
| Ovarian Cancer | 1997-2015 | $256.5 | 3,330 | 372 |
| Parkinson's | 2014-2015 | $32.0 | 25 | 54 |
| Peer-Reviewed Alzheimer's | 2014-2015 | $24.0 | 140 | 58 |
| Peer-Reviewed Cancer | 2009-2015 | $149.8 | 2,869 | 323 |
| Peer-Reviewed Medical | 1999-2006, 2008-2015 | $1,092.0 | 8,934 | 840 |
| Peer-Reviewed Orthopaedic | 2009-2015 | $278.5 | 957 | 217 |
| Prostate Cancer | 1997-2015 | $1,450.0 | 17,050 | 3,050 |
| Reconstructive Transplant | 2015 | $15.0 | 94 | 25 |
| Spinal Cord Injury | 2009-2015 | $157.9 | 778 | 163 |
| Trauma Clinical | 2014 | $5.0 | 1 | 1 |
| Tuberous Sclerosis | 2002-2006, 2008-2015 | $59.0 | 587 | 128 |
| Vision | 2013-2015 | $28.9 | 220 | 48 |
| Miscellaneous | | | | 23 |
| **Additional Supported DoD Programs/Projects** | | | | |
| Centers of Excellence | 2015 | $10.7 | n/a | 1 |
| Defense Medical Research and Development | 2010-2015 | $479.1 | 1,145 | 412 |
| Defense Medical Research and Development CSI Restoral | 2015 | $53.9 | n/a | 35 |
| Psychological Health/Traumatic Brain Injury | 2007, 2009-2015 | $820.1 | 3,345 | 485 |
| Rapid Innovation Fund | 2011-2015 | $35.7 | n/a | 15 |
| Small Business Innovation Research/ Small Business Technology Transfer | 2014-2015 | $26.0 | 44 | 98 |
| Vision Prosthesis | 2015 | $1.0 | n/a | 3 |
| **Other Submission Processes** | | | | |
| MRMC - BAA[3] | | | 144 | |
| **Total** | | **$9,736.1** | **102,002** | **14,829** |

[1] Includes awards transitioned to CDMRP with the merger.
[2] BCRS funds applications received and reviewed by the BCRP. BCRS contributed to 61 awards; 49 fully funded and 12 partially funded.
[3] 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 144 applications received, CDMRP funded 51.

# Appendix B: FY15–FY16

**Table B-1.** FY15–FY16 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 |
|---|---|---|---|
| 2015 | **$4.0M** for Alcohol and Substance Abuse Research | **Withholds**<br>USAMRMC: $79,021<br><br>**Management Costs**<br>$215,979 (5.51%) | **Research**<br>Consortium Award: $3,705,000 |
| | **Total: $4.0M** | **Total: $295,000** | **Total: $3,705,000** |
| 2016 | **$4.0M** for Alcohol and Substance Abuse Research | **Withholds**<br>USAMRMC: $60,000<br><br>**Budgeted Management Costs**<br>$275,000 (7%) | **Research**<br>Budgeted Peer-Reviewed Research: $3,665,000 |
| | **Total: $4.0M** | **Total: $335,000** | **Total: $3,665,000** |

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

**Table B-2.** FY15–FY16 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 |
|---|---|---|---|
| 2015 | **$7.5M** for Amyotrophic Lateral Sclerosis Research | **Withholds**<br>USAMRMC: $124,013<br><br>**Management Costs**<br>$431,566 (5.85%) | **Research**<br>Therapeutic Idea Award: $5,494,421<br>Therapeutic Development Award: $1,450,000 |
| | **Total: $7.5M** | **Total: $555,579** | **Total: $6,944,421** |
| 2016 | **$7.5M** for Amyotrophic Lateral Sclerosis Research | **Withholds**<br>USAMRMC: $112,500<br><br>**Budgeted Management Costs**<br>$512,500 (7%) | **Research**<br>Budgeted Peer-Reviewed Research: $6,875,000 |
| | **Total: $7.5M** | **Total: $625,000** | **Total: $6,875,000** |

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

**Table B-3.** FY15–FY16 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 |
|---|---|---|---|
| 2015 | **$6M** for Autism Research | **Withholds**<br>USAMRMC: $119,996<br><br>**Management Costs**<br>$439,118 (7.47%) | **Research**<br>Idea Development: $894,638<br>Idea Dev Multi PI: $529,446<br>Clinical Trial Award: $4,016,802 |
| | **Total: $6.0M** | **Total: $559,114** | **Total: $5,440,886** |
| 2016 | **$6M** for Autism Research | **Withholds**<br>USAMRMC: $112,500<br><br>**Budgeted Management Costs**<br>$512,500 (7%) | **Research**<br>Budgeted Peer-Reviewed Research: $6,875,000 |
| | **Total: $7.5M** | **Total: $625,000** | **Total: $6,875,000** |

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

**Table B-4.** FY15–FY16 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 |
|---|---|---|---|
| 2015 | **$3.2M** for Bone Marrow Failure Disease Research | **Withholds**<br>USAMRMC: $63,714<br><br>**Management Costs**<br>$315,118 (10.05%) | **Research**<br>Idea Development Award - Early Career Investigator: $506,368<br>Idea Development Award -Established Investigator: 2,314,800 |
| | **Total: $3.2M** | **Total: $378,832** | **Total: $2,821,168** |
| 2016 | **$3.0M** for Bone Marrow Failure Disease Research | **Withholds**<br>USAMRMC: $45,000<br><br>**Budgeted Management Costs**<br>$205,000 (7%) | **Research**<br>Budgeted Peer-Reviewed Research: $2,750,000 |
| | **Total: $3.0M** | **Total: $250,000** | **Total: $2,750,000** |

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

**Table B-5.** FY15–FY16 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 |
|---|---|---|---|
| 2015 | **$120M** for Breast Cancer Research | **Withholds**<br>USAMRMC: $2,396,630<br><br>**Management Costs**<br>$6,536,300 (5.56%) | **Research**<br>Breakthrough Award Funding Level 1: $10,953,513<br>Breakthrough Award Funding Level 2: $25,889,961<br>Breakthrough Award Funding Level 3: $7,634,845<br>Breakthrough Award Funding Level 1 Partnering PI Option: $11,821,386<br>Breakthrough Award Funding Level 2 Partnering PI Option: $28,338,615<br>Breakthrough Award Funding Level 3 Partnering PI Option: $8,571,747<br>Breakthrough Award - Funding Level 4 - Clinical Trial: $9,363,987<br>Era of Hope Scholar Award: $3,962,500<br>Distinguished Investigator Award: $4,530,516 |
| | **Total: $120M** | **Total: $8,932,930** | **Total: $111,067,070** |
| 2016 | **$120M** for Breast Cancer Research | **Withholds**<br>USAMRMC: $1,800,000<br><br>**Budgeted Management Costs**<br>$8,160,200 (7%) | **Research**<br>Budgeted Peer-Reviewed Research: $110,039,800 |
| | **Total: $120M** | **Total: $9,960,200** | **Total: $110,039,800** |

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

**Table B-6.** FY15–FY16 Breast Cancer Research Semipostal 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 |
|---|---|---|---|
| 2015 | **$536,347** in proceeds from the Stamp Out Breast Cancer Act | **Withholds**<br>USAMRMC: $0<br><br>**Management Costs**<br>$26,817 (5.00%) | **Research**<br>Breakthrough Award Funding Level 1: $254,765<br>Breakthrough Award Funding Level 1 - Partnering PI Option: $254,765 |
| | **Total: $536,347** | **Total: $26,817** | **Total: $509,530** |
| 2016 | **$568,671** in proceeds from the Stamp Out Breast Cancer Act | **Withholds**<br>USAMRMC: $0<br><br>**Budgeted Management Costs**<br>$39,800 (7%) | **Budgeted Research**<br>Budgeted Peer-Reviewed Research: $528,871 |
| | **Total: $568,671** | **Total: $39,800** | **Total: $528,871** |

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

**Table B-7.** FY15–FY16 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 |
|---|---|---|---|
| 2015 | **$3.2M** for Duchenne Muscular Dystrophy Research | **Withholds**<br>USAMRMC: $63,946<br><br>**Management Costs**<br>$413,953 (13.20%) | **Research**<br>Investigator-Initiated Research: $2,124,340<br>Translational Leverage Award: $597,761 |
| | **Total: $3.2M** | **Total: $477,899** | **Total: $2,722,101** |
| 2016 | **$3.2M** for Duchenne Muscular Dystrophy Research | **Withholds**<br>USAMRMC: $48,000<br><br>**Budgeted Management Costs**<br>$217,000 (7%) | **Budgeted Research**<br>Budgeted Peer-Reviewed Research: $2,935,000 |
| | **Total: $3.2M** | **Total: $265,000** | **Total: $2,935,000** |

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

**Table B-8.** FY15–FY16 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 |
|---|---|---|---|
| 2015 | **$7.5M** for Epilepsy Research | **Withholds**<br>USAMRMC: $149,889<br><br>**Management Costs**<br>$538,500 (7.33%) | **Research**<br>IDA - Funding Level 1: $2,417,673<br>IDA - Funding Level 2: $4,393,938 |
| | **Total: $7.5M** | **Total: $688,389** | **Total: $6,811,611** |
| 2016 | **$7.5M** for Epilepsy Research | **Withholds**<br>USAMRMC: $112,500<br><br>**Budgeted Management Costs**<br>$512,500 (7%) | **Research**<br>Budgeted Peer-Reviewed Research: $6,875,000 |
| | **Total: $7.5M** | **Total: $625,000** | **Total: $6,875,000** |

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

**Table B-9.** FY15–FY16 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 |
|---|---|---|---|
| 2015 | **$20M** for Gulf War Illness | **Withholds**<br>USAMRMC: $399,937<br><br>**Management Costs**<br>$2,610,421 (13.32%) | **Research**<br>Gulf War Illness Epidemiology Research Award: $2,171,426<br>Consortium Award: $256,827<br>Innovative Treatment Evaluation Award: $1,722,845<br>Investigator-Initiated Research Award: $5,349,980<br>New Investigator Award - New GWI Researcher: $3,093,715<br>New Investigator Award - Transitioning Postdoctoral Fellow: $886,400<br>New Investigator Award - Early-Career Investigator: $1,283,319<br>Investigator-Initiated Research Expansion Award: $697,500<br>Investigator-Initiated Research Expansion Award - Collaborative Option: $1,527,630 |
| | **Total: $20M** | **Total: $3,010,358** | **Total: $16,989,642** |
| 2016 | **$20M** for Gulf War Illness | **Withholds**<br>USAMRMC: $300,000<br><br>**Budgeted Management Costs**<br>$1,375,000 (7%) | **Research**<br>Budgeted Peer-Reviewed Research: $18,325,000 |
| | **Total: $20M** | **Total: $1,675,000** | **Total: $18,325,000** |

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

**Table B-10.** FY15–FY16 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 |
|---|---|---|---|
| 2015 | **$50M** for Joint Warfighter Medical Research | **Withholds**<br>USAMRMC: $990,110<br><br>**Management Costs**<br>$2,248,467 (4.60%) | **Budgeted Research**<br>Peer-Reviewed Research: $46,761,422 |
| | **Total: $50M** | **Total: $3,238,578** | **Total: $46,761,422** |
| 2016 | **$50M** for Joint Warfighter Medical Research | **Withholds**<br>USAMRMC: $750,000<br><br>**Budgeted Management Costs**<br>$3,447,500 (7%) | **Budgeted Research**<br>Budgeted Peer-Reviewed Research: $45,802,500 |
| | **Total: $50M** | **Total: $4,197,500** | **Total: $45,802,500** |

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

**Table B-11.** FY15–FY16 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 |
|---|---|---|---|
| 2015 | **$10.5M** for Lung Cancer Research | **Withholds**<br>USAMRMC: $209,866<br><br>**Management Costs**<br>$697,539 (6.78%) | **Research**<br>Concept Award: $1,931,143<br>Idea Development Award-Established Investigator: $1,702,781<br>Career Development Award: $1,607,791<br>Idea Development Award-New Investigator: $3,304,022<br>Clinical Exploration Award: $16,000<br>Clinical Exploration Award-Correlative Studies: $390,000<br>Expansion Award: $640,858 |
| | **Total: $10.5M** | **Total: $907,405** | **Total: $9,592,595** |
| 2016 | **$12M** for Lung Cancer Research | **Withholds**<br>USAMRMC: $180,000<br><br>**Budgeted Management Costs**<br>$820,000 (7%) | **Research**<br>Budgeted Peer-Reviewed Research: $11,000,000 |
| | **Total: $12M** | **Total: $1,000,000** | **Total: $11,000,000** |

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

**Table B-12.** FY15–FY16 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 |
|---|---|---|---|
| 2015 | **$8M** for Military Burn Research | **Withholds**<br>USAMRMC: $160,000<br><br>**Management Costs**<br>$328,926 (4.20%) | **Research**<br>Broad Agency Announcement: $1,904,501<br>Burn Injuries Research Award - Funding Level 1: $3,262,685<br>Burn Injuries Research Award - Funding Level 2: $2,343,888 |
| | **Total: $8M** | **Total: $488,926** | **Total: $7,511,074** |
| 2016 | **$8M** for Military Burn Research | **Withholds**<br>USAMRMC: $280,000<br><br>**Budgeted Management Costs**<br>$540,000 (7%) | **Research**<br>Budgeted Peer-Reviewed Research: $7,180,000 |
| | **Total: $8M** | **Total: $820,000** | **Total: $7,180,000** |

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

**Table B-13.** FY15–FY16 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 |
|---|---|---|---|
| 2015 | **$5.0M** for Multiple Sclerosis Research | **Withholds**<br>USAMRMC: $99,981<br><br>**Management Costs**<br>$355,921 (7.26%) | **Research**<br>Investigator-Initiated Partnership Award: $2,294,113<br>Pilot Clinical Trial Award: $2,249,985 |
| | **Total: $5M** | **Total: $455,902** | **Total: $4,544,098** |
| 2016 | **$6.0M** for Multiple Sclerosis Research | **Withholds**<br>USAMRMC: $90,000<br><br>**Budgeted Management Costs**<br>$410,000 (7%) | **Research**<br>Budgeted Peer-Reviewed Research: $5,500,000 |
| | **Total: $6M** | **Total: $500,000** | **Total: $5,500,000** |

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

**Table B-14.** FY15–FY16 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 |
|---|---|---|---|
| 2015 | **$15M** for Neurofibromatosis Research | **Withholds**<br>USAMRMC: $300,000<br><br>**Management Costs**<br>$1,169,228 (7.95%) | **Research**<br>Clinical Trial Award: $1,121,983<br>Exploration - Hypothesis Development Award: $688,607<br>Investigator-Initiated Research Award: $3,611,597<br>Investigator-Initiated Research Award-Optional Qualified Collaborator: $4,907,871<br>New Investigator Award: $3,200,714 |
| | **Total: $15M** | **Total: $1,469,228** | **Total: $13,530,772** |
| 2016 | **$15M** for Neurofibromatosis Research | **Withholds**<br>USAMRMC: $525,000<br><br>**Budgeted Management Costs**<br>$1,010,000 (7%) | **Research**<br>Budgeted Peer-Reviewed Research: $13,465,000 |
| | **Total: $15M** | **Total: $1,535,000** | **Total: $13,465,000** |

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

**Table B-15.** FY15–FY16 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 |
|---|---|---|---|
| 2015 | **$10M** for Orthotics and Prosthetics Outcomes Research | **Withholds**<br>USAMRMC: $198,754<br><br>**Management Costs**<br>$678,432 (6.92%) | **Research**<br>Outcome Research Award Level 1: $1,314,892<br>Outcome Research Award Level 2: $6,580,589<br>Outcome Research Award Level 2-Clinical Trial: $1,227,333 |
| | **Total: $10M** | **Total: $877,186** | **Total: $9,122,814** |
| 2016 | **$10M** for Orthotics and Prosthetics Outcomes Research | **Withholds**<br>USAMRMC: $150,000<br><br>**Budgeted Management Costs**<br>$680,000 (7%) | **Research**<br>Budgeted Peer-Reviewed Research: $9,170,000 |
| | **Total: $10M** | **Total: $830,000** | **Total: $9,170,000** |

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

**Table B-16.** FY15–FY16 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 |
|---|---|---|---|
| 2015 | **$20M** for Ovarian Cancer Research Program | **Withholds**<br>USAMRMC: $399,947<br><br>**Management Costs**<br>$1,055,231 (5.38%) | **Research**<br>Clinical Translational Leverage Award: $479,999<br>Investigator-Initiated Research Award: $3,930,750<br>Outcomes Consortium Award: $5,620,226<br>Pilot Award: $6,128,064<br>Ovarian Cancer Academy Award - Early-Career Investigators: $2,385,783 |
| | **Total: $20M** | **Total: $1,455,178** | **Total: $18,544,822** |
| 2016 | **$20M** for Ovarian Cancer Research Program | **Withholds**<br>USAMRMC: $300,000<br><br>**Budgeted Management Costs**<br>$1,375,000 (7%) | **Research**<br>Budgeted Peer-Reviewed Research: $18,325,000 |
| | **Total: $20M** | **Total: $1,675,000** | **Total: $18,325,000** |

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

**Table B-17.** FY15–FY16 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 |
|---|---|---|---|
| 2015 | **$16M** for Parkinson's Research | **Withholds**<br>USAMRMC: $320,000<br><br>**Management Costs**<br>$832,976 (5.31%) | **Research**<br>Broad Agency Announcement: $11,156,399<br>Career Progression Awards: $1,148,125<br>Depression Research Award: $2,542,500 |
| | **Total: $16M** | **Total: $1,152,976** | **Total: $14,847,024** |
| 2016 | **$16M** for Parkinson's Research | **Withholds**<br>USAMRMC: $560,000<br><br>**Budgeted Management Costs**<br>$1,080,000 (7%) | **Research**<br>Budgeted Peer-Reviewed Research: $14,360,000 |
| | **Total: $16M** | **Total: $1,640,000** | **Total: $14,360,000** |

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

**Table B-18.** FY15–FY16 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 |
|---|---|---|---|
| 2015 | **$12M** for Peer Reviewed Alzheimer's Research | **Withholds**<br>USAMRMC: $239,959<br><br>**Management Costs**<br>$725,470 (6.17%) | **Research**<br>Convergence Science Research Award: $4,743,246<br>Quality of Life Research Award: $1,390,977<br>Quality of Life Research Award - Clinical Trial: $4,900,349 |
| | **Total: $12M** | **Total: $965,428** | **Total: $11,034,572** |
| 2016 | **$15M** for Peer Reviewed Alzheimer's Research | **Withholds**<br>USAMRMC: $225,000<br><br>**Budgeted Management Costs**<br>$1,025,000 (7%) | **Research**<br>Budgeted Peer-Reviewed Research: $13,750,000 |
| | **Total: $15M** | **Total: $1,250,000** | **Total: $13,750,000** |

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

**Table B-19.** FY15–FY16 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 |
|---|---|---|---|
| 2015 | **$50M** for Peer-Reviewed Cancer Research | **Withholds**<br>USAMRMC: $981,668<br><br>**Management Costs**<br>$3,001,506 (6.12%) | **Research**<br>Colorectal: $4,163,319<br>Genetic: $2,441,180<br>Kidney: $1,348,585<br>Liver: $8,996,187<br>Melanoma & Other Skin Cancer: $11,497,718<br>Mesothelioma: $3,144,678<br>Myeloproliferative Disorders: $1,923,918<br>Neuroblastoma: $1,970,175<br>Pancreatic: $3,107,694<br>Stomach: $7,423,372 |
| | **Total: $50M** | **Total: $3,983,174** | **Total: $46,016,826** |
| 2016 | **$50M** for Peer-Reviewed Cancer Research | **Withholds**<br>USAMRMC: $750,000<br><br>**Budgeted Management Costs**<br>$3,400,000 (7%) | **Research**<br>Budgeted Peer-Reviewed Research: $45,850,000 |
| | **Total: $50M** | **Total: $4,150,000** | **Total: $45,850,000** |

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

FY15 Peer-Reviewed Cancer Research Program: The agreement provides $50,000,000 for a peer-reviewed cancer research program to research cancers not addressed in the breast, prostate, ovarian, and lung cancer research programs currently executed by the Department of Defense. The funds provided in the peer-reviewed cancer research program are directed to be used to conduct research in the following areas: colorectal cancer, genetic cancer research, kidney cancer, liver cancer, melanoma and other skin cancers, mesothelioma, myeloproliferative disorders, neuroblastoma, pancreatic cancer, and stomach cancer.

FY16 Peer-Reviewed Cancer Research Program: The agreement provides $50,000,000 for a peer-reviewed cancer research program to research cancers not addressed in the breast, prostate, ovarian, and lung cancer research programs currently executed by the Department of Defense. The funds provided in the peer-reviewed cancer research program are directed to be used to conduct research in the following areas: bladder cancer, colorectal cancer, immunotherapy, kidney cancer, listeria vaccine for cancer, liver cancer, lymphoma, melanoma and other skin cancers, mesothelioma, neuroblastoma, pancreatic cancer, pediatric brain tumors and stomach cancer.

**Table B-20.** FY15–FY16 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 |
|---|---|---|---|
| 2015 | **$247.5M** for Peer-Reviewed Medical Research | **Withholds**<br>USAMRMC: $4,949,992<br><br>**Management Costs**<br>$12,410,728 (5.12%) | **Research**<br>Acupuncture: $107,796<br>Acute Lung Injury: $13,916,633<br>Advanced Prosthetics: $1,847,828<br>Cardiovascular Health: $34,990,688<br>Chronic Migraine and Post-Traumatic Headaches: $4,513,033<br>Congenital Heart Disease: $8,890,541<br>Dengue: $4,194,634<br>Diabetes: $12,590,296<br>Focal Segmental Glomerulosclerosis: $4,970,611<br>Food Allergies: $2,561,616<br>Fragile X Syndrome: $306,000<br>Healthcare-acquired Infection Reduction: $10,182,626<br>Inflammatory Bowel Disease: $7,359,895<br>Integrative Medicine: $7,927,039<br>Interstitial Cystitis: $3,815,206<br>Lupus: $2,156,070<br>Malaria: $21,915,300<br>Metals Toxicology: $7,967,578<br>Mitochondrial Disease: $8,297,949<br>Nanomaterials for Bone Regeneration: $1,138,059<br>Neuroprosthetics: $2,628,160<br>Osteoarthritis: $1,946,995<br>Pancreatitis: $2,641,213<br>Polycystic Kidney Disease: $2,146,537<br>Post-Traumatic Osteoarthritis: $10,913,625<br>Psychotropic Medications: $500,905<br>Pulmonary Fibrosis: $3,781,191<br>Respiratory Health: $29,194,935<br>Rheumatoid Arthritis: $5,141,104<br>Scleroderma: $1,724,586<br>Sleep Disorders: $5,039,488<br>Tinnitus: $329,997<br>Vascular Malformations: $2,641,146<br>Women's Heart Disease: $1,860,000 |
| | **Total: $247.5M** | **Total: $17,360,720** | **Total: $230,139,280** |
| 2016 | **$278.7M** for Peer-Reviewed Medical Research | **Withholds**<br>USAMRMC: $4,180,500<br><br>**Budgeted Management Costs**<br>$19,019,500 (7%) | **Research**<br>Budgeted Peer-Reviewed Research: $255,500,000 |
| | **Total: $278.7M** | **Total: $23,200,000** | **Total: $255,500,000** |

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

"FY2015 Peer Reviewed Medical Research Program: The agreement provides $247,500,000 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: acupuncture, acute lung injury, advanced prosthetics, cardiovascular health, chronic migraine and post-traumatic headache, congenital heart disease, Dengue, diabetes, focal segmental glomerulosclerosis, food allergies, Fragile X syndrome, healthcare-acquired infection reduction, inflammatory bowel disease, integrative medicine, interstitial cystitis, lupus, malaria, metals toxicology, mitochondrial disease, nanomaterials for bone regeneration, neuroprosthetics, osteoarthritis, pancreatitis, polycystic kidney disease, post-traumatic osteoarthritis, psychotropic medications,

pulmonary fibrosis, respiratory health, rheumatoid arthritis, scleroderma, sleep disorders, tinnitus, vascular malformations, and women's heart disease.
FY2016 Peer Reviewed Medical Research Program: The agreement provides $278,700,000 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, chronic migraine and posttraumatic headache, congenital heart disease, constrictive bronchiolitis, diabetes, dystonia, emerging infectious diseases, focal segmental glomerulosclerosis, Fragile X syndrome, hepatitis B, hereditary angioedema, hydrocephalus, inflammatory bowel disease, influenza, integrative medicine, interstitial cystitis, lupus, malaria, metals toxicology, mitochondrial disease, nanomaterials for bone regeneration, non-opioid pain management, pancreatitis, pathogen-inactivated dried plasma, polycystic kidney disease, post-traumatic osteoarthritis, psychotropic medications, pulmonary fibrosis, respiratory health, Rett syndrome, rheumatoid arthritis, scleroderma, sleep disorders, tinnitus, tuberculosis, vaccine development for infectious disease, vascular malformations, and women's heart disease. The additional funding provided under the peer-reviewed medical research program shall be devoted only to the purposes listed above.

**Table B-21.** FY15–FY16 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 |
|---|---|---|---|
| 2015 | **$30M** for Peer-Reviewed Orthopedic Research | **Withholds**<br>USAMRMC: $599,910<br><br>**Management Costs**<br>$1,251,907 (4.26%) | **Research**<br>Applied Research Award - Funding Level 1: $1,997,483<br>Applied Research Award - Funding Level 2: $3,783,226<br>Clinical Consortium Award: $3,558,726<br>Clinical Trial Award: $1,962,417.00<br>Orthopaedic Care and Rehabilitation Consortium Award: $16,846,331 |
| | **Total: $30M** | **Total: $1,851,817** | **Total: $28,148,183** |
| 2016 | **$30M** for Peer-Reviewed Orthopedic Research | **Withholds**<br>USAMRMC: $450,000<br><br>**Budgeted Management Costs**<br>$2,050,000 (7%) | **Research**<br>Budgeted Peer-Reviewed Research: $27,500,000 |
| | **Total: $30M** | **Total: $2,500,000** | **Total: $27,500,000** |

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

**Table B-22.** FY15–FY16 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 |
|---|---|---|---|
| 2015 | **$80M** for Prostate Cancer Research | **Withholds**<br>USAMRMC: $1,594,656<br><br>**Management Costs**<br>$4,749,884 (6.06%) | **Research**<br>Clinical Consortium Award: $2,426,119<br>Clinical Consortium Award - Clinical Research Site: $2,467,813<br>Collaborative Undergraduate HBCU Student Summer Training Program Award: $1,394,393<br>Health Disparity Research Award - Established Investigator: $1,784,471<br>Health Disparity Research Award - Established Investigator with Qualified Collaborator Option: $2,017,646<br>Idea Development Award - Established Investigator - Partnering PI Option: $17,388,943<br>Idea Development Award - New Investigator: $3,466,021<br>Idea Development Award-Established Investigator: $14,032,952<br>Impact Award: $3,278,335<br>Impact Award - Clinical Trial: $1,179,426<br>Impact Award - Clinical Trial - Partnering PI Option: $3,139,998<br>Impact Award - Partnering PI Option: $12,464,364<br>Physician Research Training Award: $3,074,569<br>Postdoctoral Training Award: $3,901,058<br>Prostate Cancer Pathology Resource Network Award: $1,639,352 |
| | **Total: $80M** | **Total: $6,344,540** | **Total: $73,655,460** |
| 2016 | **$80M** for Prostate Cancer Research | **Withholds**<br>USAMRMC: $1,200,000<br><br>**Budgeted Management Costs**<br>$5,450,000 (7%) | **Research**<br>Budgeted Peer-Reviewed Research: $73,350,000 |
| | **Total: $80M** | **Total: $6,650,000** | **Total: $73,350,000** |

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

**Table B-23.** FY15–FY16 Peer Reviewed 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 |
|---|---|---|---|
| 2015 | **$15M** for Peer Reviewed Reconstructive Transplant Research | **Withholds**<br>USAMRMC: $298,704<br><br>**Management Costs**<br>$690,560 (4.70%) | **Research**<br>Concept Award: $991,851<br>Idea Discovery Award: $6,289,655<br>Translational Research Award: $998,776<br>Studies Option $349,000<br>Technology/Therapeutic Development Award: $2,846,693<br>Military Medical Research and Development Award: $2,534,761 |
| | **Total: $15M** | **Total: $989,264** | **Total: $14,010,736** |
| 2016 | **$12M** for Peer Reviewed Reconstructive Transplant Research | **Withholds**<br>USAMRMC: $180,000<br><br>**Budgeted Management Costs**<br>$820,000 (7%) | **Research**<br>Budgeted Peer-Reviewed Research: $11,000,000 |
| | **Total: $12M** | **Total: $1,000,000** | **Total: $11,000,000** |

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

**Table B-24.** FY15–FY16 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 |
|---|---|---|---|
| 2015 | **$30M** for Spinal Cord Injury Research | **Withholds**<br>USAMRMC: $599,910<br><br>**Management Costs**<br>$2,602,551 (8.85%) | **Research**<br>Investigator-Initiated Research Award: $4,592,578<br>Clinical Trial Award: $13,272,074<br>Translational Research Award - Optional Qualified Collaborator: $8,185,677<br>Qualitative Research Award: $747,210 |
| | **Total: $30M** | **Total: $3,202,461** | **Total: $26,797,539** |
| 2016 | **$30M** for Spinal Cord Injury Research | **Withholds**<br>USAMRMC: $450,000<br><br>**Budgeted Management Costs**<br>$2,050,000 (7%) | **Research**<br>Budgeted Peer-Reviewed Research: $27,500,000 |
| | **Total: $30M** | **Total: $2,500,000** | **Total: $27,500,000** |

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

**Table B-25.** FY16 Tick-Borne Disease Research Program CDMRP Executed Funds, Management Costs, and Execution of Investment Strategy

| Fiscal Year | Congressional Language and Appropriations | Withholds and Management Costs | Investment Strategy |
|---|---|---|---|
| 2016 | **$5.0M** Tick-Borne Disease Research | **Withholds**<br>USAMRMC: $75,000<br><br>**Budgeted Management Costs**<br>$340,000 (7%) | **Research**<br>Budgeted Peer-Reviewed Research: $4,585,000 |
| | **Total: $5.0M** | **Total: $415,000** | **Total: $4,585,000** |

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

**Table B-26.** FY16 Trauma Clinical Research Program CDMRP Executed Funds, Management Costs, and Execution of Investment Strategy

| Fiscal Year | Congressional Language and Appropriations | Withholds and Management Costs | Investment Strategy |
|---|---|---|---|
| 2016 | **$10.0M** Trauma Clinical Research | **Withholds**<br>USAMRMC: $150,000<br><br>**Budgeted Management Costs**<br>$680,000 (7%) | **Research**<br>Budgeted Peer-Reviewed Research: $9,170,000 |
| | **Total: $10.0M** | **Total: $830,000** | **Total: $9,170,000** |

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

**Table B-27.** FY15–FY16 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 |
|---|---|---|---|
| 2015 | **$6M** for Tuberous Sclerosis Complex Research | **Withholds**<br>USAMRMC: $119,861<br><br>**Management Costs**<br>$388,952 (6.61%) | **Research**<br>Exploration - Hypothesis Development Award: $1,376,962<br>Idea Development Award: $1,417,777<br>Idea Development Award - Optional Qualified Collaborator: $2,696,448 |
| | **Total: $6M** | **Total: $508,813** | **Total: $5,491,187** |
| 2016 | **$6M** for Tuberous Sclerosis Complex Research | **Withholds**<br>USAMRMC: $90,000<br><br>**Budgeted Management Costs**<br>$410,000 (7%) | **Research**<br>Budgeted Peer-Reviewed Research: $5,500,000 |
| | **Total: $6M** | **Total: $500,000** | **Total: $5,500,000** |

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

**Table B-28.** FY15–FY16 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 |
|---|---|---|---|
| 2015 | **$10M** for Vision Research | **Withholds**<br>USAMRMC: $199,108<br><br>**Management Costs**<br>$613,596 (6.26%) | **Research**<br>Technology/Therapeutic Development Award: $8,974,148<br>Clinical Trial Award: $213,148 |
| | **Total: $10M** | **Total: $812,704** | **Total: $9,187,296** |
| 2016 | **$10M** for Vision Research | **Withholds**<br>USAMRMC: $150,000<br><br>**Budgeted Management Costs**<br>$680,000 (7%) | **Research**<br>Budgeted Peer-Reviewed Research: $9,170,000 |
| | **Total: $10M** | **Total: $886,000** | **Total: $9,170,000** |

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

**Table B-29.** FY15 Centers of Excellence 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 |
|---|---|---|---|
| 2015 | **$10.7M** for Breast Cancer COE, Gynecological Cancer COE, and Integrated Cardiac Health Project COE | **Management Costs**<br>$446,864 (3.70%) | **Research**<br>Breast Cancer COE: $3,869,865<br>Gynecological Cancer COE: $3,294,865<br>Integrated Cardiac Health Project COE: $3,116,664 |
| | **Total: $10.7M** | **Total: $446,864** | **Total: $10,281,394** |

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

**Table B-30.** FY15 Defense Medical Research and Development Program CDMRP Executed Funds, Management Costs, and Execution of Investment Strategy

| Fiscal Year | Congressional Language and Appropriations | Withholds and Management Costs | Investment Strategy |
|---|---|---|---|
| 2015 | **$157.3M** for Defense Medical Research and Development from the Guidance for the Development of the Force Funding and Restore Core Research Funding | **Management Costs**<br>$10,831,970 (6.89%) | **Research**<br>Medical Simulation and Information Sciences Awards: $29,516,839<br>Military Infectious Diseases Awards: $4,795,811<br>Military Operational Medicine Awards: $23,211,508<br>Combat Casualty Care Awards: $43,255,691<br>Clinical and Rehabilitative Medicine Awards: $43,655,072<br>Clinical Research Intramural Initiative: $2,066,000 |
| | **Total: $157.3M** | **Total: $10,831,970** | **Total: $146,500,922** |

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

**Table B-31.** FY15 Psychological Health/Traumatic Brain Injury Research Program CDMRP Executed Funds, Management Costs, and Execution of Investment Strategy

| Fiscal Year | Congressional Language and Appropriations | Withholds and Management Costs | Investment Strategy |
|---|---|---|---|
| 2015 | **$82.6M** for Psychological Health and Traumatic Brain Injury Research | **Management Costs** $4,526,832 (5%) | **Research**<br>Military Operational Medicine Awards: $39,234,306<br>Combat Casualty Care Awards: $18,525,053<br>Clinical and Rehabilitative Medicine Awards: $20,297,920 |
| | **Total: $82.6M** | **Total: $4,526,832** | **Total: $78,057,279** |

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

**Table B-32.** FY15 Rapid Innovation Fund CDMRP Executed Funds, Management Costs, and Execution of Investment Strategy

| Fiscal Year | Congressional Language and Appropriations | Withholds and Management Costs | Investment Strategy |
|---|---|---|---|
| 2015 | **$5.0M** for Rapid Innovation Fund | **Management Costs** $182 | **Research**<br>Rapid Innovation Fund: $5,013,686 |
| | **Total: $5.0M** | **Total: $182** | **Total: $5,013,686** |

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

**Table B-33.** FY15 Small Business Innovation Research/Small Business Technology Transfer Program CDMRP Executed Funds, Management Costs, and Execution of Investment Strategy

| Fiscal Year | Congressional Language and Appropriations | Withholds and Management Costs | Investment Strategy |
|---|---|---|---|
| 2015 | **$11.2M** DHP and Army SBIR and STTR | | **Research**<br>DHP: $9,200,321<br>Army: $2,018,430 |
| | **Total: $11.2M** | | **Total: $11,218,751** |

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

**Table B-34.** FY15 Vision Prosthesis Program CDMRP Executed Funds, Management Costs, and Execution of Investment Strategy

| Fiscal Year | Congressional Language and Appropriations | Withholds and Management Costs | Investment Strategy |
|---|---|---|---|
| 2015 | **$1.0M** Army Funded Vision Prosthesis | **Management Costs** $71,253 | **Research**<br>Vision Prosthesis Pilot Study Awards: $928,744 |
| | **Total: $1.0M** | **Total: $71,253** | **Total: $928,744** |

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

# Appendix C: Breast Cancer Research Semipostal Awards FY99–FY15

| Fiscal Year | Principal Investigator | Amount | Institution | Proposal Title |
|---|---|---|---|---|
| FY99 | Daly | $283,649 | Garvan Institute | Identification of Novel Prognostic Indicators for Breast Cancer through Analysis of the EMS1/Cortactin Signaling Pathway |
| | Deuel | $5,000[1] | Scripps Institute | Novel Angiogenic Domains: Use in Identifying Unique Transforming and Tumor-Promoting Pathways in Human Breast Cancer |
| | Heyer | $111,444 | University of California, Davis | In Vitro Recombination Activities of the Breast Cancer Predisposition Protein BRCA2 |
| | Musgrove | $222,652 | Garvan Institute | Role of Cyclin D1 and p27 in Steroidal Control of Cell Cycle Progression in the Mammary Gland in Vivo |
| | Shah | $279,000 | University of Arkansas | Role of a Novel Matrix-Degrading Metalloproteinase in Breast Cancer Invasion |
| | Wang | $317,510 | Texas A&M University | Scanning Microwave-Induced Acoustic Tomography |
| | 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 |
| | Wreschner | $225,000 | Tel Aviv University | Analysis of the Secreted Novel Breast Cancer-Associated MUC1/Zs Cytokine |
| FY00 | Adamson | $578,183 | Burnham Institute | Cripto: A Target for Breast Cancer Treatment |
| | Akporiaye | $454,500 | University of Arizona | Tumor-Mediated Suppression of Dendritic Cell Vaccines |
| | Penn | $296,142 | University of Toronto | Exploiting the Novel Repressed Transactivator Assay to Identify Protein Interactors and Peptide Inhibitors of the Myc Oncoprotein |
| FY01 | Cai | $560,144 | Vanderbilt University | Genetic Polymorphisms, Mitochondrial DNA Damage, and Breast Cancer Risk |
| | Carraway | $427,225 | University of California, Davis | Identification of a Functional Human Homolog of Drosophila Kek1, an Inhibitor of Breast Tumor Cell Growth |
| | Chaudhary | $312,000 | University of Texas Southwest Medical Center | The Role of Ectodysplasin A (EDA) and Its Receptors in the Pathogenesis of Breast Cancer |
| | Geahlen | $425,425 | Purdue University | Characterization of Syk in Breast Carcinoma Cells |
| | Rosner | $454,181 | St. Luke's-Roosevelt Hospital Center | Autocrine and Paracrine Control of Breast Cancer Growth by Sex Hormone-Binding Globulin |
| FY02 | 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 |
| | Godwin | $504,000 | Fox Chase Cancer Center | The Nuclear Death Domain Protein p84N5, a Candidate Breast Cancer Susceptibility Gene |
| | Perkins | $490,500 | Yale University | Rapid Genomic Approach to Cancer Gene Discovery in Breast Cancer |
| FY03 | 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 |
| | 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) |
| | Yaswen | $508,790 | Lawrence Berkeley National Laboratory | Functional Analysis of BORIS, a Novel DNA-Binding Protein |
| | Ziv | $767,171 | University of California, San Francisco | Admixture and Breast Cancer Risk among Latinas |

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

| Fiscal Year | Principal Investigator | Amount | Institution | Proposal Title |
|---|---|---|---|---|
| FY04 | Bissell | $386,569 | Lawrence Berkeley National Laboratory | Use of HA-Metal Nanoparticles to Identify and Characterize Tumorigenic Progenitor Cell Subsets in Breast Tumors |
| | 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 |
| | Giorgio | $453,000 | Vanderbilt University | Surface Functionalized Nanoparticles and Nanocrystals for Proximity-Modulated, Early Neoplasia Detection, Imaging, and Treatment of Breast Cancer |
| | Lemmon | $475,500 | University of Pennsylvania | Harnessing Novel Secreted Inhibitors of EGF Receptor Signaling for Breast Cancer Treatment |
| FY05 | Zinn[2] | $436,500 | University of Alabama at Birmingham | Novel Screening and Precise Localization of Early Stage Breast Cancer in Animal Model |
| | Huang | $483,600 | Cornell University, Weill Medical College | Migrastatin Analogues as Potent Inhibitors of Breast Cancer Metastasis |
| | Liu | $448,500 | Ohio State University | Hunting for Novel X-Linked Breast Cancer Suppressor Genes in Mouse and Human |
| | Rao | $468,000 | Stanford University | Ribozyme-Mediated Imaging of Oncogene Expression in Breast Tumor Cells |
| FY06 | Devi | $155,085[3] | Duke University Medical Center | Modulation of Regulatory T Cells as a Novel Adjuvant for Breast Cancer Immunotherapy |
| | Lee | $489,000 | University of Southern California | A New Mechanism for Estrogen-Starvation Resistance in Breast Cancer |
| | Li | $438,455 | Baylor College of Medicine | The ER/PR Status of the Originating Cell of ER-Negative Breast Cancer |
| | Mousa | $377,620 | Albany College of Pharmacy | Enhancing the Efficacy of Chemotherapeutic Breast Cancer Treatment with Non-anticoagulant Heparins |
| | Rastinejad | $454,500 | University of Virginia | Structural Characterization of the Interdomain Features of the Estrogen Receptor |
| FY07 | Kuperwasser | $817,500 | Tufts University | Mechanisms of Breast Cancer Associated with Obesity |
| | Kelly | $244,450[4] | University of Virginia | Genetically Encoded Targeted, Amplifiable, Imaging Agents for Early Detection of Breast Cancer |
| | Gerbi | $155,550[5] | Brown University | Hormonal Involvement in Breast Cancer Gene Amplification |
| FY08 | Park | $111,663 | North Dakota State University | In Utero Exposure to Dietary Methyl Nutrients and Breast Cancer Risk in Offspring |
| | Radosz | $528,939 | University of Wyoming | Breast Cancer-Targeting Nuclear Drug Delivery Overcoming Drug Resistance for Breast Cancer Therapy |
| | Hill | $577,500 | Oregon Health and Science University | Vaccine Vector for Sustained High-Level Antitumor CTL Response |
| | You | $503,666 | University of Oklahoma Health Science Center | Targeted Delivery and Remote-Controlled Release of Chemotherapeutic Agents |
| | Seagroves | $166,667[6] | University of Tennessee Health Science Center | The Role of HIF-1 Alpha in Breast Cancer: A Positive Factor in Cancer Stem Cell Expansion via Notch? |
| FY09 | Reynolds | $730,000[7] | Cancer Prevention Institute of California | Hazardous Air Pollutants and Breast Cancer: An Unexplored Area of Risk |
| | Wysolmerski | $620,626 | Yale University | Effects of Nuclear Parathyroid Hormone-Related Protein Signaling in Breast Cancer |
| FY10 | Schedin | $368,125[8] | University of Colorado, Denver | The Immune Modulatory Program of Post-Partum Involution Promotes Pregnancy-Associated Breast Cancer |
| | Leung | $556,875[9] | Johns Hopkins University | The Role of Poly(ADP-Ribose) in microRNA Activity in Breast Cancers |

[2]The original Principal Investigator, Dr. Tandra Chaudhuri, is deceased.

[3]Total award amount was $461,933; remaining funds were from the FY06 BCRP.

[4]Total award amount was $687,397 remaining funds were from the FY06 BCRP.

[5]Total award amount was $787,325; remaining funds were from the FY06 and FY07 BCRP.

[6]Total award amount was $554,987; remaining funds were from the FY08 BCRP.

[7]Total award amount was $860,883; remaining funds were from the FY09 BCRP.

[8]Total award amount was $556,028; remaining funds were from the FY10 BCRP.

[9]Total award amount was $585,652; remaining funds were from the FY10 BCRP.

| Fiscal Year | Principal Investigator | Amount | Institution | Proposal Title |
|---|---|---|---|---|
| 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 |

[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.

# Appendix D: Acronyms

AD.....Alzheimer's disease
ADMET.....adsorption, distribution, metabolism, excretion, and toxicity
ADNI..... Alzheimer's Disease Neuroimaging Initiative
ADPKD.....autosomal-dominant polycystic kidney disease
ADRD..... Alzheimer's Disease and Related Dementia
AFIRM.....Armed Forces Institute of Regenerative Medicine
ALS..... Amyotrophic Lateral Sclerosis
ALSRP.....Amyotrophic Lateral Sclerosis Research Program
AON..... antisense oligonucleotides
AR..... androgen receptor
ARP.....Autism Research Program
ASADRP.....Alcohol and Substance Abuse Disorders Research Program
ASD..... autism spectrum disorder
ASK1..... Apoptosis signal-regulating kinase 1
ASUD..... alcohol and substance abuse disorder
AUD.....alcohol use disorder
B.....billion
BAA..... Broad Agency Announcement
BADER.....Bridging Advanced Developments for Exceptional Rehabilitation
BCRP.....Breast Cancer Research Program
BCRS.....Breast Cancer Research Semipostal
BDI.....Beck Depression Inventory
BICU.....Burn Intensive Care Unit
BMFRP..... Bone Marrow Failure Research Program
BMI..... brain machine interface
CAP.....Consortium to Alleviate Post-Traumatic Stress Disorder
CAPS.....Clinician Administered PTSD Scale
CAR.....chimeric antigen receptors
CARE..... Concussion Assessment, Research, and Education
CCCRP..... Combat Casualty Care Research Program
CCNE1.....Cyclin E1
CCTD.....Chronic Caprine Tibial Defect
CDK..... cyclin-dependent kinase
CDMRP.....Congressionally Directed Medical Research Programs
CENC..... Chronic Effects of Neurotrauma Consortium
CNS.....central nervous system
COACH.... Combined Online Assistance for Caregiver Health
CoQ10.....Coenzyme Q10
CRMRP.....Clinical and Rehabilitative Medicine Research Program
CRPC.....castration-resistant prostate cancer
CURE.....Citizens United for Research in Epilepsy
D-22..... decinium-22
DHA..... Defense Health Agency
DHP..... Defense Health Program
DMDRP .. Duchenne Muscular Dystrophy Research Program
DMRDP.....Defense Medical Research and Development Program
DoD.....Department of Defense
DTC.....disseminated tumor cell
eBRAP..... Electronic Biomedical Research Application Portal
ECI.....Early-Career Investigator
EGS..... Electronic Grants System
ER.....endoplasmic reticulum
ER+..... estrogen receptor-positive
ERP.....Epilepsy Research Program
FAO.....fatty acid oxidation
FDA..... U.S. Food and Drug Administration
FY.....fiscal year
GEM.....genetically engineered mouse
GM.....gray matter
GWI..... Gulf War Illness
GWIRP..... Gulf War Illness Research Program
GWVIRP.....Gulf War Veterans' Illnesses Research Program
HAP.....hazardous air pollutants
HDAC.....histone deacetylase
HGSC..... high-grade serous carcinoma
HGSOC..... high-grade serous ovarian cancer
HHS..... Department of Health and Human Services
HMD..... Health and Medicine Division
HNF4A..... hepatocyte nuclear factor
Hpo..... Hippo
HSC..... hematopoietic stem cell
IBD..... irritable bowel disease
ICG..... Indocyanine Green
IIRA..... Investigator-Initiated Research Award
IMU..... inertial measurement unit
IND.....Investigational New Drug
iNPG..... injectable nanoparticle generator
INTRuST.....INjury and TRaumatic STress
IOM.....Institute of Medicine
ITN.....Institute for Translational Neuroscience
JPC.....Joint Program Committee
JWMRP..... Joint Warfighter Medical Research Program
LCRP..... Lung Cancer Research Program
LIC.....leukemia-initiating cell

LITES..... Linking Investigations in Trauma and Emergency Services
LTI..... Liberating Technologies, Inc.
M.....million
MBRP .....Military Burn Research Program
MDS.....myelodysplastic syndrome
METRC.....Major Extremity Trauma Research Consortium
MHS.....Military Health System
MIDRP .....Military Infectious Diseases Research Program
miRNA .....microRNA
MOCOG...Multidisciplinary Ovarian Cancer Outcomes Group
MOMRP..... Military Operational Medicine Research Program
MRI .....magnetic resonance imaging
mRNA.....messenger RNA
mTBI .....mild traumatic brain injury
MS ..... multiple sclerosis
MSIS.....Medical Simulation and Information Sciences
MSRC .....Military Suicide Research Consortium
MSRP .....Multiple Sclerosis Research Program
mTOR ..... mammalian target of rapamycin
NAS ..... National Academies of Sciences, Engineering, and Medicine
NCAA.....National Collegiate Athletic Association
NF..... neurofibromatosis
NF1..... neurofibromatosis type 1
NFCTC .....Neurofibromatosis Clinical Trials Consortium
NFRP..... Neurofibromatosis Research Program
NIH .....National Institutes of Health
NIR .....near-infrared
NIR-OI .....NIR optical imaging
NIRS .....near-infrared spectroscopy
OASD(HA).....Office of the Assistant Secretary of Defense for Health Affairs
OCA.....Ovarian Cancer Academy
OCCA ..... Ovarian Cancer Consortium Award
OCRP ..... Ovarian Cancer Research Program
OEF ..... Operation Enduring Freedom
OIF.....Operation Iraqi Freedom
OPORP.....Orthotics and Prosthetics Outcomes Research Program
PA .....Program Announcement
PAD ..... Program Area Directorates
PARS ..... Parkinson's Associated Risk Syndrome
PASA ..Pharmacotherapies for Alcohol and Substance Abuse
PCa.....prostate cancer
PCCTC ..... Prostate Cancer Clinical Trials Consortium
PCRP.....Prostate Cancer Research Program
PD.....Parkinson's disease
pDox ..... polymeric Doxorubicin
PEDF .....pigmentary epithelium-derived factor
PET.....positron emission tomography
PH..... psychological health
PH/TBIRP ..... Psychological Health and Traumatic Brain Injury Research Program
PI ..... Principal Investigator
PLA..... polylactide-coglycolide acid
PNES.....Psychogenic Non-Epileptic Seizures
POIP ..... Phases of Illness Paradigm
PR+ .....progesterone receptor-positive
PRARP .....Peer Reviewed Alzheimer's Research Program
PRCRP .....Peer Reviewed Cancer Research Program
PRMRP.....Peer Reviewed Medical Research Program
PRORP..... Peer Reviewed Orthopaedic Research Program
PRP .....Parkinson's Research Program
PSA.....prostate-specific antigen
PTBP1 .....polypyrimidine tract-binding protein 1
PTE.....post-traumatic epilepsy
PTSD ..... post-traumatic stress disorder
R&A ..... Review & Analysis
R&D ..... Research and Development
RAMBA.....retinoic acid metabolism blocking agent
Rb ..... retinoblastoma
RFP ..... Request for Proposals
RHERP ..... Radiation Health Effects Research Program
RNA.....ribonucleic acid
RTI.....Research Triangle Institute
RTRP.....Reconstructive Transplant Research Program
SBIR ..... Small Business Innovation Research
SCI.....spinal cord injuries
SCIRP.....Spinal Cord Injury Research Program
SDS .....Shwachman Diamond syndrome
SERT .....serotonin transporter
SLN.....sentinel lymph node
SOC.....standard of care
SOD.....super oxide dismutase
sPA .....photoacoustic
STIC ..... serous tubal intraepithelial carcinoma
STRONG STAR..... South Texas Research Organizational Network Guiding Studies on Trauma and Resilience
STTR .....Small Business Technology Transfer
SUD .....substance use disorder
TAPTE ..... Team Approach to the Prevention and Treatment of Post-Traumatic Epilepsy
TBI ..... traumatic brain injury
TBDRP ..... Tick-Borne Disease Research Program
TED ..... Traumatic Brain Injury Endpoints Development
TIVA.....Total Intravenous Anesthesia
TNBC..... triple-negative breast cancer
TRL..... technology-readiness level

TSA..... Trichostatin A
TSC ..... tuberous sclerosis complex
TSCRP .....Tuberous Sclerosis Complex Research Program
TSH ..... thyroid-stimulating hormone
US.....ultrasound
USAMRAA.. U.S. Army Medical Research Acquisition Activity
USAMRMC .....U.S. Army Medical Research and Materiel Command
UTMB .....University of Texas Medical Branch at Galveston
VA .....U.S. Department of Veterans Affairs
VCA ..... vascularized composite allotransplantation
VRP .....Vision Research Program
WET.....whole-eye transplantation
WRC .....Wake Forest-led Warrior Restoration Consortium
Wts ..... Warts

For more information, visit: **http://cdmrp.army.mil**

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