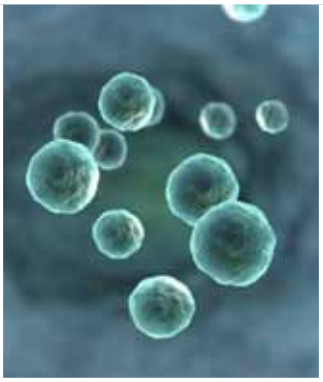
CDMRP
Department of Defense

Congressionally Directed Medical Research Programs

ANNUAL REPORT
SEPTEMBER 30, 2014





U.S. Army Medical Research and Materiel Command

Letter from the Director

As the Director of the Congressionally Directed Medical Research Programs (CDMRP), I am pleased to present to you the 2014 Annual Report. Over the course of the past year, the CDMRP and the funding program of the Telemedicine and Advanced Technology Research Center (TATRC) have merged in order to meet the challenges and needs of the military to advance and sustain medical capabilities through research for Service Members, their families, and the American public.

The merger of two outstanding funding programs under the auspices of the U.S. Army Medical Research and Materiel Command (USAMRMC) demonstrates a dedication to a synergy of purpose with increased efficiency for military and health research initiatives. The Annual Report illustrates the transparency of our processes and our partnership with the USAMRMC Joint Program Committees, consumer advocates, and the scientific community at large.

The CDMRP is devoted to its vision to find and fund the best research to improve the lives of those who serve our country, of those who support our Service Members, and for those whom the military protects, the American public. This Annual Report was developed through the dedication, devotion, and promise that the CDMRP and its staff impart every day in their work ethic and in their commitment to the military, the families, and the public.

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

Department of Defense

U.S. Army Medical Research and Materiel Command

Congressionally Directed Medical Research Programs

Annual Report

September 30, 2014

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Introduction

The U.S. Army Medical Research and Materiel Command (USAMRMC) mission to responsively and responsibly create, develop, deliver, and sustain medical capabilities for the Warfighter by leading the advancement of military medicine is achieved through innovative management and execution of funds. The office of the Congressionally Directed Medical Research Programs (CDMRP) implements the investment of core dollars (presidential budgetary monies) and congressionally directed monies by funding groundbreaking, high-impact research awards and contracts. Over the course of fiscal year 2014 (FY14), two of the major management organizations of USAMRMC, the CDMRP and the research funding program of the Telemedicine and Advanced Technology Research Center (TATRC), are joining forces to handle the research funding execution and management. The merger of these outstanding organizations will create efficiencies and synergies of processes and research initiatives to support and fund the best scientific research for the Warfighter and the American public.

This merger may be envisioned as a meeting of two great organizations bringing together the best of both: CDMRP's excellence in review and management of awards fused with TATRC's exceptional ability to respond to the needs of the military. This ideal collaboration will help to ensure that only the best research is funded for both our military and civilian populations (see **Figure 1**).

With the creation of the new execution and management organization, the scope of funded programs has expanded to meet critical research needs. Currently funded research programs include the following:

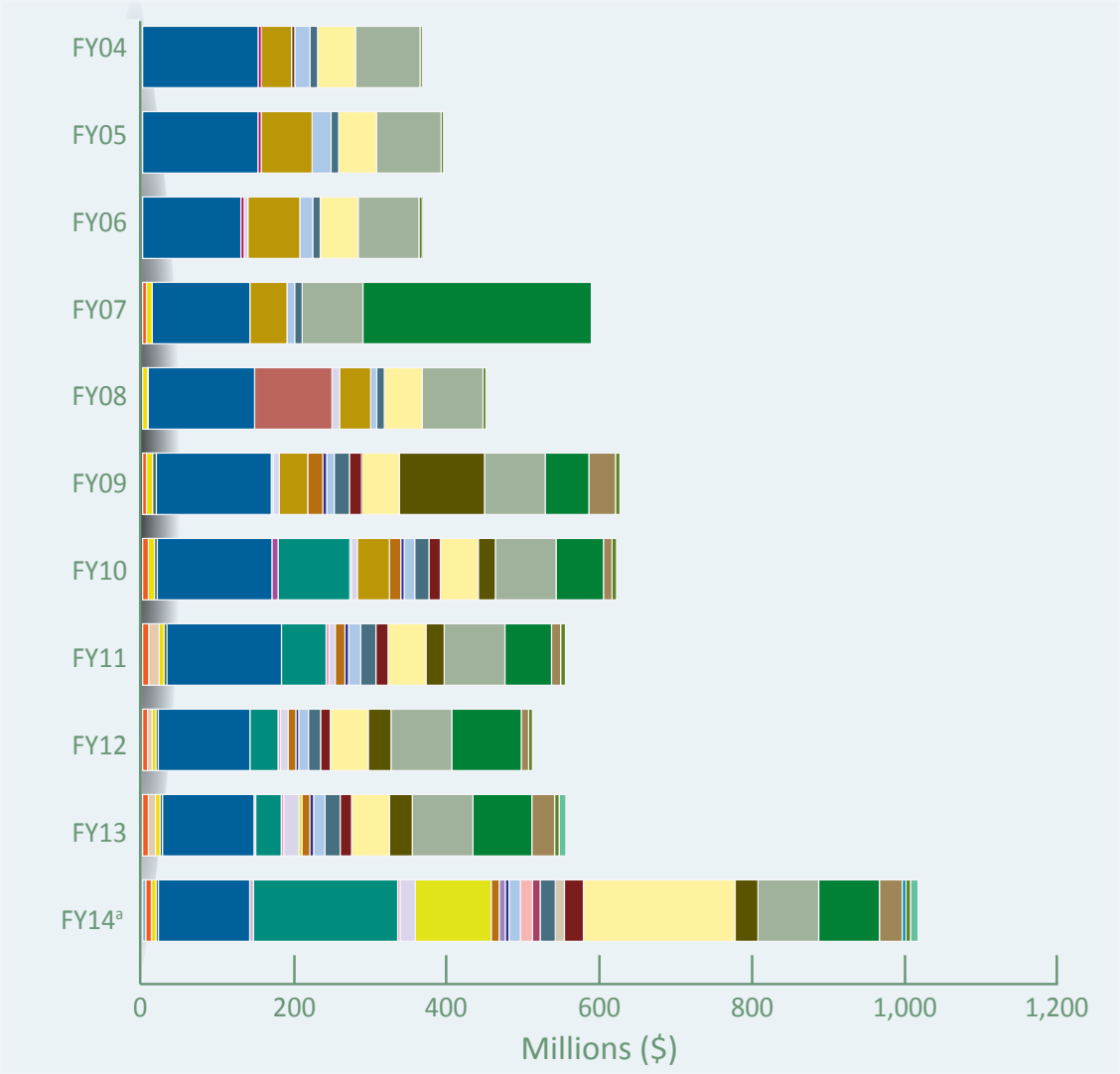
- Alcohol and Substance Abuse
- Amyotrophic Lateral Sclerosis
- Autism
- Bone Marrow Failure
- Breast Cancer
- Breast Cancer Semipostal
- Defense Medical Research and Development
- Duchenne Muscular Dystrophy
- Gulf War Illness
- Joint Warfighter Medical
- Lung Cancer
- Military Burn
- Multiple Sclerosis
- Neurofibromatosis
- Neurotoxin Exposure Treatment Parkinson's
- Orthotics and Prosthetics Outcomes
- Ovarian Cancer
- Peer Reviewed Alzheimer's
- Peer Reviewed Cancer
- Peer Reviewed Medical
- Peer Reviewed Orthopaedic
- Prostate Cancer
- Psychological Health and Traumatic Brain Injury
- Spinal Cord Injury
- Trauma Clinical Research Repository
- Tuberous Sclerosis Complex
- Vision

VISION

Find and fund the best research to eradicate diseases and support the Warfighter for the benefit of the American public

MISSION

Provide hope by promoting innovative research, recognizing untapped opportunities, creating partnerships, and guarding the public trust



- Alcohol and Substance Abuse Disorders
- Amyotrophic Lateral Sclerosis
- Army Rapid Innovation Fund
- Autism
- Bone Marrow Failure Disorder
- Breast Cancer
- Chiropractic Clinical Trials
- Chronic Myelogenous Leukemia
- Clinical Research Intramural Initiative
- Cooperative DoD/VA Medical
- Defense Medical R&D (DHPe)
- Defense Women's Health
- Deployment Related Medical
- Duchenne Muscular Dystrophy
- Genetic Studies of Food Allergies
- Gulf War Illness
- Institutionally Based Programs
- Joint Warfighter Medical Research
- Lung Cancer
- Military Burn Program
- Multiple Sclerosis
- Myeloproliferative Disorders
- National Prion
- Neurofibromatosis
- Neurotoxin Exposure Treatment Parkinson's
- Orthotics and Prosthetics Outcomes
- Osteoporosis
- Ovarian Cancer
- Peer Reviewed Alzheimer's
- Peer Reviewed Cancer
- Peer Reviewed Medical
- Peer Reviewed Orthopaedic
- Prostate Cancer
- Psychological Health/Traumatic Brain Injury
- Spinal Cord Injury
- Trauma Clinical Research Repository
- Tuberous Sclerosis Complex
- Vision

Figure 1. FY04–FY14[b, c] Research Funding Programs

Data as of September 30, 2014. Investment of FY14 funds will be complete as of September 30, 2015.

[a] Does not include amounts of Defense Health Program Core, and Psychological Health and Traumatic Brain Injury funding executed on behalf of the Joint Program Committee that is currently estimated at $40 million.

[b] Funding history for prior years can be found on our website at http://cdmrp.army.mil/about/fundinghistory.

[c] TATRC programs are included only for FY14.

Programs

Highlights of current programs managed and/or executed can be found within the program pages in this Annual Report, beginning on page 32. As detailed in **Table 1**, in FY14, the CDMRP completed the execution of FY13 appropriations by processing 621 new awards across 22 programs. In addition, in FY14, the CDMRP and TATRC initiated the management of $1,021.72 million (M) across 24 programs, as well as execution of another 4 programs on behalf of other organizations.

Table 1. CDMRP Programs, Appropriations, and Applications Received and Awarded

Programs Managed by the CDMRP[a]	FY13				FY14	
	Funds Received (in millions)	Applications Received	Applications Funded	Funding Modifications Completed	Funds Received (in millions)	Applications Received to Date
Alcohol and Substance Abuse Disorders[b]					$4.00	TBD
Amyotrophic Lateral Sclerosis	$7.50	61	7	-	$7.50	57
Autism	$6.00	93	17	-	$6.00	TBD
Bone Marrow Failure	$3.20	30	5	-	$3.20	37
Breast Cancer/Breast Cancer Research Semipostal	$120.60	1,521	107	-	$120.32	933
Duchenne Muscular Dystrophy	$3.20	11	3	-	$3.20	TBD
Gulf War Illness	$20.00	52	16	2	$20.00	TBD
Joint Warfighter Medical Research[b]					$100.00	103
Lung Cancer	$10.50	407	29	1	$10.50	353
Military Burn[b]					$8.00	TBD
Multiple Sclerosis	$5.00	36	6	-	$5.00	39
Neurofibromatosis	$15.00	89	19	-	$15.00	66
Neurotoxin Exposure Treatment Parkinson's[b]					$16.00	TBD
Orthotics and Prosthetics Outcomes[b]					$10.00	TBD
Ovarian Cancer	$20.00	157	29	1	$20.00	159
Peer Reviewed Alzheimer's[b]					$12.00	TBD
Peer Reviewed Cancer	$15.00	181	27	-	$25.00	223
Peer Reviewed Medical	$50.00	523	50	2	$200.00	385
Peer Reviewed Orthopaedic	$30.00	114	28	-	$30.00	TBD
Prostate Cancer	$80.00	1,127	161	2	$80.00	868
Spinal Cord Injury	$30.00	83	26	3	$30.00	TBD
Trauma Clinical Research Repository[b]					$5.00	TBD
Tuberous Sclerosis	$6.00	55	10	-	$6.00	44
Vision[b]					$10.00	TBD
Programs Executed on Behalf of Others[c]						
Army Rapid Innovation Fund	$9.38	-	4	-	TBD	TBD
Clinical Research Intramural Initiative	$2.23	4	3	-	$5.00	TBD
Defense Medical Research & Development	$33.68	143	15	43	$190.00	137
Joint Warfighter Medical Research	$3.95	2	2	-	-	-
Psychological Health/Traumatic Brain Injury	$77.51	110	45	-	$80.00	8
Vision	$8.92	142	12	-	-	-
Total	**$557.67**	**4,941**	**621**	**54**	**$1,021.72**	**3,412**

[a] CDMRP executed and managed the full appropriation.
[b] TATRC program newly included as of FY14.
[c] CDMRP assisted with execution of the specified portion of a larger appropriation(s).

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 U.S. Department of Defense (DoD), researchers, advocate communities, and the public. Programs follow the management cycle described in detail on the following pages, but do so with consideration of the requirements and needs of each program's stakeholders. Each step in the execution and management cycle is depicted in Figure 2.

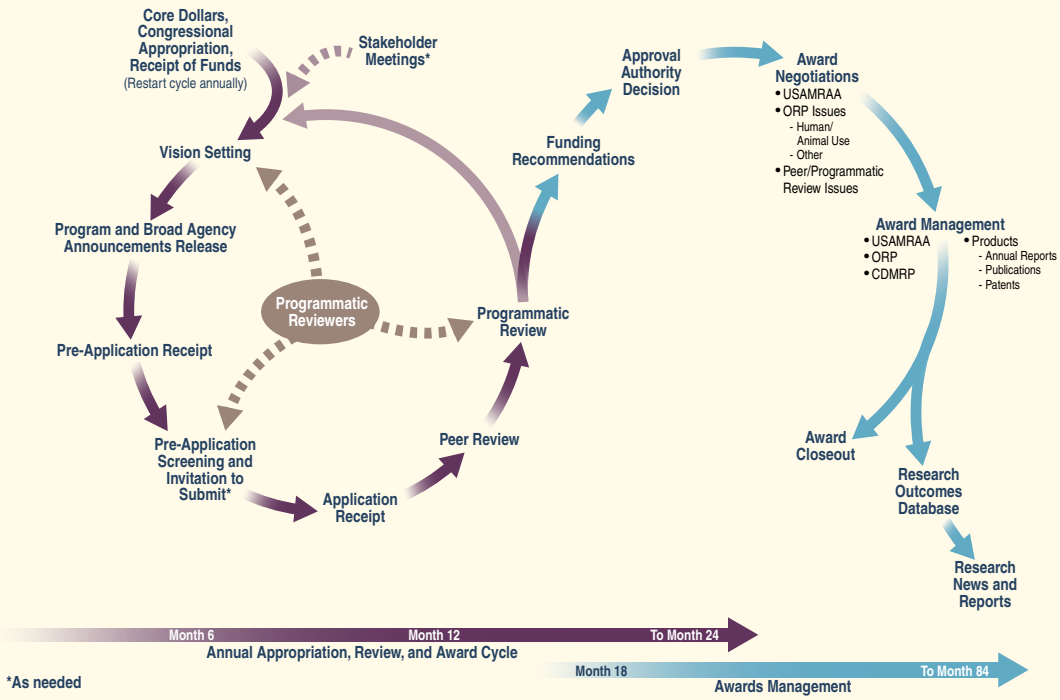


Figure 2. Execution and Management Cycle

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 and do not take away any monies to fund the Warfighter. The Defense Health Program also includes funds for military medical research from the President's budget or core dollars. Over the years, both the CDMRP and TATRC have been the main organizations within USAMRMC to execute and manage these research funding dollars.

2. Vision Setting

Based on the recommendations of the National Academy of Sciences Institute of Medicine (IOM), each research program holds an annual vision setting meeting to identify scientific research gaps for the program year. The process of vision setting brings together experts in science, the clinic, and the military, as well as the layperson to discuss the knowledge gaps in the program-specific areas. The vision setting process concludes with an expert review of the scientific needs to be formulated into an investment strategy that encourages research in knowledge gaps and underrepresented areas. Program announcements/funding opportunities are offered and represent the most needed areas of scientific research for the program year.

3. Program Announcements and Broad Agency Announcements

The award mechanisms are released as program announcements or Broad Agency Announcements (BAAs), depending on the program. Both of these solicitations provide applicants details about a particular award mechanism, 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.

4. Applicant Submission and Receipt

For many of the award mechanisms, application submission requires a multistep process consisting of a pre-application submission (which includes a letter of intent, pre-proposal, and/or nomination) followed by full application submission. The pre-application is an abbreviated submission outlining the research aims, strategy, innovation, and/or impact of the project. Pre-applications may be screened by either the programmatic reviewers or a peer review panel, based on the requirements described in each program announcement or BAA. The final product of the screening is a recommended list of invited applicants. As summarized in **Table 2**, in FY14, the CDMRP received 10,469 pre-applications and nominations that, after screening and invitation, resulted in 3,728 full applications received as of the date of this report. In addition, the CDMRP and TATRC received 2,484 full applications from mechanisms that did not require pre-applications or nominations, for a total of 6,212 full applications received to date.

Table 2. Number of Submissions Received
October 1, 2013–September 30, 2014, across FY13–FY14 Programs

Mechanism Submissions	
Pre-proposals or nominations screened	10,469
Letters of intent received	3,059
Total pre-applications received	**13,528**
Full Application Submissions	
Full applications from invitations only	3,728
Full applications from letter of intent	2,484
Total full applications received	**6,212**

5. Two-Tier Review Process

The two-tier review of applications is based on the recommendations set forth by the IOM committee in 1993. The two tiers of review are peer review and programmatic review. Every application is given a fair and balanced review, taking steps to ensure that conflicts of interest do not influence the process, and the needs of the Warfighter and the general public are taken into account. Additional details regarding the two tiers of review can be accessed on the CDMRP website at http://cdmrp.army.mil/about/fundingprocess.

Peer Review: Peer review is a criteria-based process where applications are evaluated based on their scientific and technical merit. The peer review panel evaluates each application based on the review criteria outlined in the program announcement or BAA, and rates the various criteria numerically. Each application is evaluated for its own merit, independent of other applications. The product of peer review is a summary statement that describes the strengths and weaknesses of the application in accordance with the published review criteria and includes an overall peer review score.

Programmatic Review: After applications have been peer reviewed, the applications go through a process of programmatic review by experts, including scientists, clinicians, military members, and/or laypersons. At the programmatic review level, the peer review summary statement, in addition to criteria published in the funding opportunity (program announcement or BAA), is compared and assessed for programmatic relevance, portfolio balance, and scientific merit. 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.

Less than 1% of applicants voice objections regarding the scientific peer review or programmatic review of their applications. An Inquiry Review Panel addresses applicant queries. These appeals must be based on the occurrence of errors at receipt, peer review, or programmatic review. If an error is identified, the application will be sent for re-review at the appropriate level (peer and/or programmatic review).

Multistep Process to Minimize Award Duplication and Overlap

- List of past, current, and pending funding support submitted by the PI at the time of application submission.
- Identification of project innovation, research duplication, and overlap during the two-tier review process by peers in the field.
- List of updated funding support at the time of award notification, which is certified by the award recipient's Sponsored Programs Office.
- Review of submitted documents and research program sites to assess pending and existing funding support during award negotiations.
- Technical review of progress throughout the award period of performance, which includes funding overlap and duplication.

6. 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, USAMRMC, and/or the Director of the Defense Health Agency, Research, Development and Acquisition 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.

7. Award Negotiations and Management

Negotiation and management of awards are a major focus of the USAMRMC offices and organizations, including the CDMRP, U.S. Army Medical Research Acquisition Activity (USAMRAA), and Office of Research Protections (ORP). During the period of performance for awards (which can be up to 5 years), the CDMRP actively manages and monitors progress. The awards management process is depicted in **Figure 3**. Approximately 500 to 600 new awards are made each fiscal year. As of September 30, 2014, CDMRP has managed 12,423 awards through its funding history.

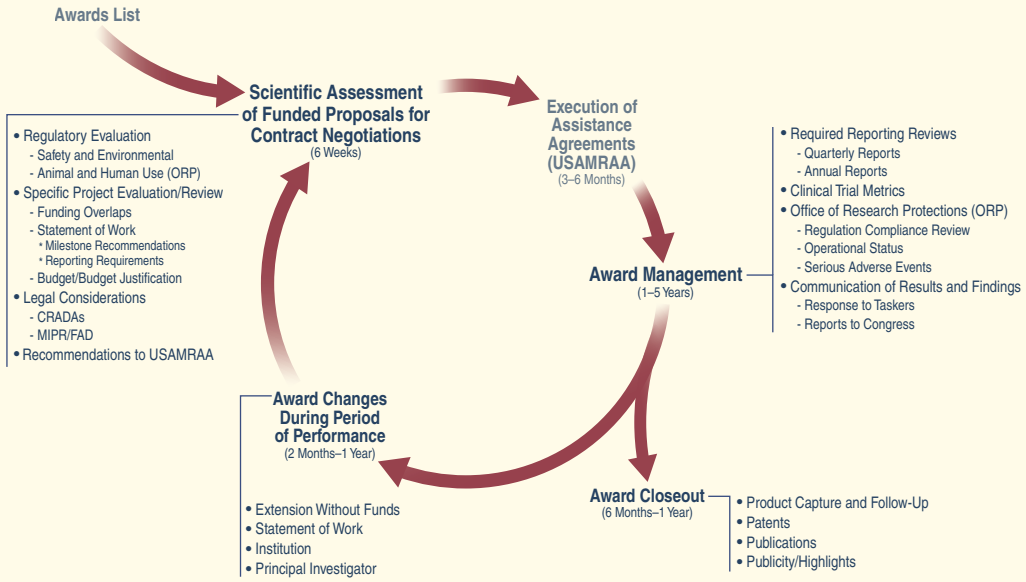


Figure 3. Execution and Management Cycle

Each award is assigned a Science Officer (SO). The SO serves as the technical representative for the lifetime of the award. The SO also acts as a liaison, maintaining the proper flow of information between the awardee institution, the Principal Investigator (PI), the program office, and offices within USAMRMC. Formal analysis of the budget with respect to the scope of work to be performed is completed to ensure cost sharing when possible and avoidance of overlap in research funding with other funding agencies. Once all aspects of negotiation are complete, an award is signed and an assistance agreement (grant or cooperative agreement) or contract is issued. The life-cycle management of awards continues throughout the period of performance with monitoring of the technical progress, regulatory review, and financial reporting. At a minimum, all funded PIs are required to submit annual progress reports and quarterly financial reports. The progress of larger complex awards and consortia may also be monitored through external advisory boards, site visits, teleconferences, and other meetings throughout the entire period of performance.

8. Award Closeout

Award closeout takes place at both USAMRAA and the program office, and this is usually performed 6 months after the period of performance has expired. During this time, the CDMRP and TATRC carefully monitor the final progress report and the patent report, while USAMRAA reviews the final financial accounting. Actions regarding any patents, invention disclosures, publications, and follow-up funding are captured during award closeout. When significant discoveries are identified, the awards are flagged for further follow-up.

9. Research News and Reports/Public Relations

To be transparent to the public, various communication processes and social media techniques are used to communicate with stakeholders and audiences. The website remains a central mode of communication to the public, featuring videos, press releases, research highlights, consumer stories, program books, annual reports, and abstracts 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/.

Since FY13, social media has been utilized as another means to expand CDMRP's information dissemination strategies. YouTube has been a popular source to access videos about the funded research programs and funded investigators (http://www.youtube.com/user/CDMRP). Twitter users can subscribe or follow tweets at https://twitter.com/CDMRP.

Automated Business Processes

Two important electronic business systems are used in the receipt of applications, and negotiation and management of awards. These automated business processes enable multiple users to input data, download information, and manage the daily administrative tasks associated with application submission and grant processing in centralized, secure locations. As a result, users experience increased efficiency in data management throughout application submission and administration of awards.

Electronic Biomedical Research Application Portal (eBRAP)	Electronic Grants System (EGS)
• Worldwide web-based accessibility for receipt and processing of pre-applications and full applications, and documents required for award negotiations. • Computer-automated processes associated with program announcement release, as well as batch retrieval, processing, modification, and compliance of full applications. • Capability enabling researchers to review and modify application components (submitted to Grants.gov). • Capability to communicate with research community on a one-to-one basis in batches.	• Enables real-time electronic workflow and transfer of data among offices of USAMRMC. • Multiple users are able to input data, download reports, and manage daily administrative tasks associated with grants processing in a central, secure location. • During management of awards, research outcomes and findings are entered and categorized in EGS, and then subsequently analyzed by staff for program evaluation efforts, interacting with funded investigators, and reporting to stakeholders. • The website automatically retrieves public information from EGS to provide up-to-date information on funded awards to end users and the public.

eBRAP is a research pre-application and full application processing and management tool.

EGS is a business system designed primarily to manage funded awards, allowing multiple organizations to view and access award data and files generated during the life of an award.

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, as well as fostering real-time communication and research results. Highlights of ongoing consortia are provided in the following sections.

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 post-traumatic stress disorder (PTSD). The STRONG STAR team of approximately 100 military, civilian, and Department of Veterans Affairs (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 11 collaborating investigators from across the country. The goal of the STRONG STAR Consortium is to reduce or eliminate combat-related PTSD in active duty military and recently discharged veterans. The STRONG STAR Consortium is conducting 13 projects, including one animal study, retrospective data analyses, epidemiological studies, a data repository, a biorepository, and 10 clinical studies. The results of many 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 2015.

PTSD and TBI Clinical Consortium Award – INTRuST

The INjury and TRaumatic STress Consortium (INTRuST) was established to combine the research efforts of the Nation's leading experts on PTSD and traumatic brain injury (TBI) to bring to market novel treatments or interventions for those who suffer from PTSD and/or TBI. The INTRuST Consortium is composed 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. Entering its seventh year, the INTRuST Consortium is enrolling subjects in one final core trial and an additional three final pilot clinical trials. Enrollment is now complete, and data analysis is under way or complete, for six core trials and two pilot clinical trials. 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, and their caregivers, and the American public. In addition, the repositories will serve as a resource for future investigators, providing blood and DNA/RNA samples, as well as neuroimages, of clinical trial subjects for future use. 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.

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 psychological health (PH)/TBI funding, which began in 2008, the goal of Mission Connect is to improve the diagnosis and treatment of mild TBI (mTBI) through collaborative basic and clinical research. Over the past 6 years, Mission Connect has made many 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 magnetic resonance imaging (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 (fMRI) biofeedback protocol that improves the function of damaged neural networks of mTBI patients. Investigators have evaluated 10 therapeutic agents in animal models of mTBI characterized and standardized by Mission Connect. One of the most promising agents, ARA290, will be developed further using funding from the National Institutes of Health (NIH) and an industry partner.

The Consortium to Alleviate Post-Traumatic Stress Disorder

The Consortium to Alleviate PTSD (CAP) is a cutting-edge, joint VA and DoD effort to understand and treat PTSD and related conditions in active duty military Service Members and veterans. CAP has two main objectives: one focusing on the advancement of treatment strategies for PTSD, including interventions for early, chronic, and latent onset cases, and one to identify and confirm clinically relevant biomarkers as diagnostic and prognostic indicators of PTSD and co-occurring disorders. Research within CAP focuses across a range of topics, including behavioral health disorders, mood and anxiety disorders, sexual dysfunction, neurologic disorders, pain, cognitive deficits, and neuroendocrine deficits. CAP is led by PI and Director Dr. Alan Peterson of the University of Texas Health Science Center, San Antonio, and Co-Director Dr. Terry Keane of the VA Boston Healthcare System. Currently, 17 institutions across the United States participate in CAP; additional information can be found at http://delta.uthscsa.edu/consortiumtoalleviateptsd/.

The Chronic Effects of Neurotrauma Consortium

The Chronic Effects of Neurotrauma Consortium (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. In addition, 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. CENC is led by PI Dr. David Cifu at Virginia Commonwealth University and Co-Directors Dr. Ramon Diaz-Arrastia at the Uniformed Services University of the Health Sciences and Dr. Rick Williams at RTI International. Currently, CENC leverages collaborations among 18 participating institutions across academia, industry, DoD, and 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.

Ovarian Cancer Academy

In FY09, a Dean and seven Early-Career Investigator (ECI) Awards marked the realization of the Ovarian Cancer Research Program's (OCRP) vision of a unique, virtual Ovarian Cancer Academy that supports the development of career ovarian cancer researchers. This Academy brings together a group of talented and highly committed ECIs with their mentors and an Academy Dean. 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. The Academy has expanded to currently include 11 ECI–Mentor pairs, and the ECIs have demonstrated remarkable progress, including over 160 publications and over 100 abstracts to date focused on ovarian cancer. Their growth as independent, committed ovarian cancer researchers is evident in the 49 funded grants obtained (including NIH R01s), as well as their service on the boards of well-established journals and women's cancer foundations. Additionally, in the span of 4 years, the 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 Ovarian Cancer Academy in-person workshop in Seattle, Washington, in September 2014 promoted further collaborations and fostered cross-mentoring within the group of ECIs. It preceded the Marsha Rivkin Ovarian Cancer Research Symposium, wherein several Academy members were invited speakers and all had poster presentations.

Prostate Cancer Clinical Trials Consortium

The Prostate Cancer Clinical Trials Consortium (PCCTC) has received support from the Prostate Cancer Research Program (PCRP) since 2005 and, in February 2014, filed paperwork to become a limited liability company (Prostate Cancer Clinical Trials Consortium, LLC). Led by Memorial Sloan Kettering Cancer Center, PCCTC has completed 106 clinical trials, and an additional 42 trials are still active or pending activation. Over 4,380 patients have been enrolled in these trials, with 13% representing patients from minority 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 end points for prostate cancer clinical trials. These recommendations have had a profound impact on the clinical research community and how clinical trials are designed; the Consortium is currently working on releasing an update to this effort. 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 U.S. Food and Drug Administration (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, preventing transcription of AR-regulated genes. Other promising agents advanced to Phase III testing include 1) ARN-509, another androgen antagonist showing even greater efficacy than enzalutamide; 2) dasatinib, a tyrosine kinase inhibitor; 3) the CYP17A1 inhibitor orteronel; 4) two immunotherapies: cixutumumab, which targets insulin-like growth factor-1 receptor, and ipilimumab, an antibody that binds to the T-cell-specific molecule CTLA4; and 5) tasquinimod, an angiogenic inhibitor that prevents cancer cell growth by inhibiting the growth of new blood vessels.

Neurofibromatosis Clinical Trials Consortium

The Neurofibromatosis Clinical Trials Consortium (NFCTC) has been developing clinical trials for the treatment of neurofibromatosis (NF) complications, including plexiform neurofibromas, cognitive disorders, low-grade gliomas, vestibular schwannomas, and malignant peripheral nerve sheath tumors (MPNSTs). NFCTC is composed of an Operations Center at the University of Alabama at Birmingham, 13 clinical sites, and five collaborating sites to improve geographical coverage and inclusion of adults and children with NF type 1 (NF1) and type 2 (NF2), and schwannomatosis. Four studies were funded by the FY06 Consortium Award and are nearing completion. An additional three trials were funded by the FY11 Consortium Award, and a fourth trial is in the planning stage.

NFCTC is also leveraging information from the NF Preclinical Consortium funded by the Children's Tumor Foundation to help develop a pipeline of drug trials that will be tested by NFCTC. Additional details can be found at http://cdmrp.army.mil/nfrp/.

Bridging Advanced Developments for Exceptional Rehabilitation Consortium

The Bridging Advanced Developments for Exceptional Rehabilitation (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. Clinical trials addressing lower-extremity trauma are currently aimed at improving step-to-step control during walking, improving limb-loading on the prosthetic and the intact limb via gait training, 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 prosthesis, as well as 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.

Gulf War Illness Consortia

The Gulf War Illness Consortia (GWIC) is led by Dr. Kimberly Sullivan of Boston University and brings together established Gulf War Illness (GWI) researchers across the Nation to investigate the pathobiological mechanisms responsible for GWI symptoms as they relate to brain-immune interactions. This consortium will undertake 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. Investigations will include clinical case-control studies examining markers in the blood and brain fluid, brain imaging, and memory testing. Parallel preclinical studies will evaluate persistent effects of Gulf War neurotoxicants in vitro and in rodent models of GWI. Results from this integrated approach should lead to a rational and efficient basis for identifying diagnostic markers and beneficial treatments for GWI.

Detection of Early Lung Cancer Among Military Personnel Consortium

The Detection of Early Lung Cancer Among Military Personnel (DECAMP) 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 DECAMP 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, and 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, and the second is developing and testing new noninvasive molecular biomarkers in the airway and blood to identify those smokers at highest risk for developing lung cancer.

Ovarian Cancer Consortium Award

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 the Johns Hopkins University, along with collaborators at the gynecologic oncology powerhouses of Memorial Sloan Kettering Cancer Center, 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, 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 (HGSCs), 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, and a fifth epidemiological study designed to evaluate whether these STIC characteristics are modifiable by oral contraceptives or anti-inflammatory agents.

Several major accomplishments of the Consortium are as follows:

- Verified several new identifying markers in STICs.
- Identified a putative pre-malignant precursor to STICs, known as STILs, or serous tubal intraepithelial lesions, and are examining the gain or loss of markers in STILs, STICs, and HGSCs.
- Made progress in evaluating whether the presence of a STIC is associated with different clinical manifestations and/or outcomes as compared to patients in whom STICs were not identified.
- Identified molecular changes preceding STICs in high-risk women using in vitro and in vivo models. The latest discoveries were presented at the 5th Annual Ovarian Cancer Symposium on the Prevention and Early Detection of Ovarian Cancer, held in September 2014 at the Princess Margaret Cancer Center in Toronto.

Understanding Gulf War Illness: An Integrative Modeling

An integrative modeling approach under the leadership of Dr. Mariana Morris, Dr. Nancy Klimas, and Dr. Gordon Broderick, this Gulf War Illness Research Program (GWIRP) Consortium represents expertise in neurotoxicology, animal modeling, computational modeling, clinical research, and drug development. The integrated research team aims to develop a translational model of GWI that will rapidly identify molecular targets and predict effective therapeutic interventions. The work of the Consortium will center on five studies, starting with characterizing autonomic neural/adrenal dysfunction, and cellular and molecular phenotypes in a mouse model of GWI, and will lead to generation of translational animal and human data to support clinical Phase I investigations. Computational studies will be implemented in tandem to compare mouse and human regulatory networks, support potential clinical strategies, and simulate treatment effects. The integrated approach under this Consortium provides an excellent opportunity for advancing GWI diagnosis and treatment.

Vital Partnerships

Throughout the years, partnerships with the consumer and scientific communities, professional organizations, and military communities have been fostered to continue 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.

Looking Ahead

The new initiative to merge the two major funding components of USAMRMC, the CDMRP and the research funding arm of TATRC, will enhance the ability to answer the needs of the Defense Health Program. Dedicated scientists, administrators, and Service Members working together will increase synergy, decrease Government overlap of activities, and help to accomplish the vision and mission of USAMRMC.

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 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 peer review panels by the lay organizations. Similar to 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. Scientists are involved in the day-to-day management of the individual programs and grants. 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. For example, more than 160 scientists, clinicians, and professionals are involved in all phases of program management. 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 FY14, nearly 275 consumers served on CDMRP peer review panels and approximately 40 served as programmatic reviewers.

In FY14, more than 1,475 scientists and clinicians provided necessary subject matter expertise on peer review panels and more than 175 scientists and clinicians served as programmatic reviewers. As of September 30, 2014, over 240 ad hoc reviewers have been recruited to FY14 panels. Since its inception, approximately 9,210 researchers have been funded by the CDMRP to improve the health and quality of life of all people.

Today, nearly 2,000 consumers have represented their communities and lay organizations at least once since 1992, and their role continues to be vital.

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. Ensuring against duplication and encouraging complementary investment strategies are accomplished by inviting members of other federal and non-federal agencies to participate in the peer and programmatic review of applications, as well as serve on review boards to monitor and oversee the progress of awards. These interagency collaborations strive toward synergy with other agencies and diversification of funded research portfolios, underscoring the importance of research coordination efforts. Examples of interagency collaborations include the following:

Advisory Committee on Breast Cancer in Young Women

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

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 U.S. Department of Health and Human Services 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 Breast Cancer and Environmental Research Coordinating Committee

A congressionally mandated group co-chaired by the National Institute of Environmental Health Sciences and the National Cancer Institute that has made recommendations to the Secretary of Health and Human Services on federal research efforts in the areas of environmental research and prevention of breast cancer.

Interagency Urology Coordinating Committee

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

International Cancer Research Partners

A group of 56 cancer-funding organizations that work together to enhance the impact of research to benefit all individuals affected by cancer through global collaboration and strategic coordination of research.

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.

Trans-Agency Early-Life Exposures and Cancer Working Group

A working group composed of representatives from NIH, CDC, and the CDMRP. The group's goals are: 1) stimulating and facilitating research on early-life events/exposures and cancer within the context of the missions of the federal agencies; 2) planning and hosting lecture series to foster awareness, stimulate new scientific interest, and generate transdisciplinary

Current interagency collaborations include...

- Advisory Committee on Breast Cancer in Young Women
- Federal Interagency Traumatic Brain Injury Research Working Group
- Foundation Allied Support Group
- Interagency Autism Coordinating Committee
- Interagency Breast Cancer and Environmental Research Coordinating Committee
- Interagency Urology Coordinating Committee
- International Cancer Research Partners
- Muscular Dystrophy Coordinating Committee
- Trans-Agency Early-Life Exposures and Cancer Working Group
- Trans-NIH Neurofibromatosis Working Group
- Tuberous Sclerosis Alliance

DoD SBIR/ STTR Program Objectives...

- Stimulate technological innovation.
- Increase private-sector commercialization of federal R&D.
- Increase small business participation in federally funded R&D.
- Foster participation by minority and disadvantaged firms in technological innovation.

collaborations among intramural and extramural research communities; and 3) conducting portfolio analysis to address current research funding portfolios on early-life events/ exposures and cancer, and to determine gaps and future needs.

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 & Small Business Technology Transfer Research Programs

The Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) Programs are competitive funding opportunities designed to strengthen the role of innovative small businesses in federally funded research and development (R&D). Established 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. Eleven federal agencies participate in the SBIR program and five participate in the STTR program, including 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. In FY13, a Phase II contract was awarded to Physical Optics Corporation to study nano-therapeutics and peripheral neuropathy through the SBIR program. In FY14, SBIR awards of more than $4.5M have been awarded, and more than $900,000 has been awarded for STTR.

Military Partnerships

U.S. Army Medical Research and Materiel Command

The CDMRP is located within USAMRMC, the largest medical research organization within DoD. USAMRMC is responsible for managing medical research programs that address both military and civilian groups. 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. 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 DoD. Non-core programs are funded through congressional-line-item additions to the DoD budget. The CDMRP executes 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 executed by the CDMRP have the potential to become fielded products for our Warfighters. USAMRMC has designed and implemented a process called Decision Gate to effectively manage medical materiel development in a cost-effective, consistent, and transparent process. Decision Gate is grounded in the DoD Directive 5000 series, FDA regulations, and best industry practices, and it allows USAMRMC to remain responsive to the changing needs of the Warfighter. Projects funded by 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 a technology-readiness level (TRL) code to them. The TRL system tracks product progress from basic research and technology development through manufacturing, production,

Figure 4. The USAMRMC Team

USAMRMC's MISSION: Responsively and responsibly create, develop, deliver, and sustain medical capabilities for the Warfighter

VISION: Lead the advancement of military medicine

and deployment. This information is used by USAMRMC to determine whether any CDMRP-funded projects meet Decision Gate criteria. If a CDMRP-funded project meets Decision Gate criteria, it will be entered into the Decision Gate process, a point called the Materiel Development Decision. Once in Decision Gate, product development will be managed by an Integrated Product Team (IPT). Science Officers from the CDMRP are often asked to participate on the IPTs due to their scientific expertise and relationship to the product developer. As the product matures, it will go through a series of decision points (called milestones) to determine whether it should continue as planned, continue with a revised plan, or have its development terminated (see **Figure 5** for the life cycle of a medical product). There are three decision points, called Milestones A, B, and C, which roughly correspond with Phase I clinical trial, Phase II clinical trial, and FDA approval, respectively. The Decision Gate process reflects USAMRMC's commitment to remain a good steward of taxpayer dollars and a world-class medical research and development organization.

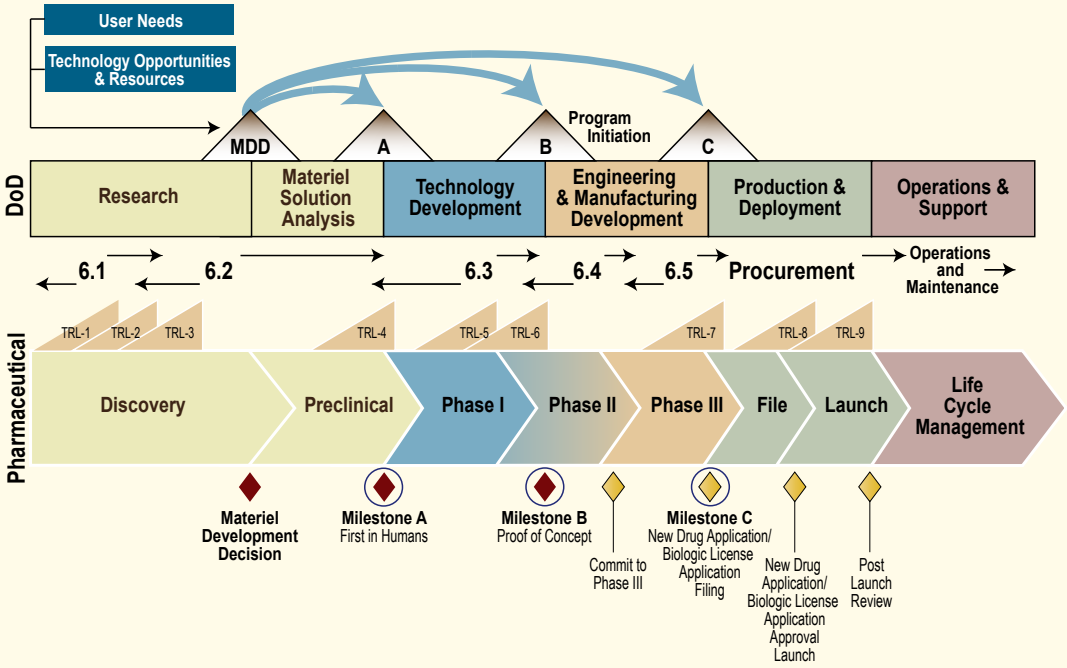


Figure 5. Decision Gate Life Cycle

Joint Program Committees

The Defense Medical Research and Development Program (DMRDP) is the research arm of the Defense Health Program within the OASD(HA). 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 DMRDP, see pages 44–45.) Joint Program Committees (JPCs) are advisory bodies composed of medical and military experts that provide funding recommendations and program management support for DMRDP-funded research. The CDMRP works with the JPCs to execute a number of extramural programs. The combined effort leverages the CDMRP's expertise in research program administration with the JPCs' technical and strategic expertise for the advancement of the DMRDP mission to expedite the delivery of products and solutions that address challenges related to Service Members and their families. In FY14, the CDMRP assisted with program execution in a number of areas relevant to battlefield injury and military service, including basic and applied psychological health, PTSD, TBI, neurotrauma, neuroplasticity, wound infections, infectious diseases, prosthetics, vision, hearing, balance, and other rehabilitative and regenerative medicine efforts. This partnership supports the CDMRP's vision of finding and funding the best research to support the Warfighter and the American public.

U.S. Department of Veterans Affairs

In support of the August 31, 2012, Presidential Executive Order 13625, DoD and the VA have combined more than $100M in a collaborative effort to fund two new consortia aimed at improving diagnosis and treatment of mTBI and PTSD. These consortia include CAP and CENC. These collaborative efforts are described in further detail on page 10 of this Annual Report. In addition, the CDMRP coordinates with the VA to enrich projects within GWIRP. GWIRP is collaborating with the VA to make the best possible use of available resources in support of high-quality, veteran-focused research on GWI (see pages 48–49 for additional details on GWIRP). VA scientists and clinicians serve on both peer and programmatic review panels for GWIRP to inform and help make funding recommendations, as well as to provide valuable resources and expertise as investigators on many GWIRP-funded awards.

CDMRP... Advancing Scientific Research

PARTNERSHIPS

Spinal Cord Injury Research Program

Drs. Gordon Mitchell, Gillian Muir, and ***Randy Trumbower***, through a multi-institutional collaborative effort, obtained preliminary clinical evidence that daily mild intermittent hypoxia (dAIH), and dAIH combined with overground walking, improve walking speed and endurance in persons with chronic, incomplete spinal cord injury (SCI).

Lung Cancer Research Program

Dr. Avrum Spira and ***Dr. Peter Schnall***. Early detection of malignant lung lesions in the potentially curable stages is essential to improving the prognosis and long-term survival of lung cancer patients. In an effort to support development of improved methods for early detection of lung cancer, the Lung Cancer Research Program (LCRP) provided support to establish the DECAMP clinical consortium, where the four largest military medical treatment facilities in the United States, along with seven VA hospitals and additional clinical sites, formed a partnership to develop and improve the process of diagnosing individuals at high risk of developing lung cancer.

Prostate Cancer Research Program

Dr. Howard Scher and team. PCCTC (www.pcctc.org) was initiated in 2006, bringing together 10 renowned cancer centers, led by Dr. Howard Scher, to speed up clinical testing of new drugs for prostate cancer. PCCTC added more sites in 2008 and 2014 to reach its current size of 15 members, and in 2014 launched a new independent entity, the Prostate Cancer Clinical Trials Consortium, LLC. To date, PCCTC has accrued more than 4,200 prostate cancer patients to more than 139 Phase I and Phase II clinical trials studying 88 new drugs, generating over 160 peer-reviewed abstracts and 60 manuscripts. PCCTC rapidly advanced 10 therapeutic candidates to Phase III clinical testing, including abiraterone acetate (ZYTIGA) and enzalutamide (XTANDI), both now FDA-approved and part of the standard of care for the treatment of advanced prostate cancer.

TECHNOLOGICAL ADVANCES

Breast Cancer Research Program

Dr. Laurie Fajardo and ***Dr. Daniel Kopans***. The Breast Cancer Research Program (BCRP) provided support to optimize technology and to conduct a multicenter clinical validation of digital mammography. The study demonstrated that digital mammography is superior to film mammography in detecting breast cancer in women with dense breast tissue, leading to a change in clinical practice. BCRP also supported the development and clinical evaluation of digital breast tomosynthesis. This three-dimensional (3D) digital mammography tool offers an additional 3D view to capture images for improved sensitivity. A tomosynthesis system is now FDA approved and commercialized for clinical use.

The Advancements in Scientific Research for the 2014 Annual Report do not include outcomes from the funding program of TATRC. For further information on the research funded by TATRC, see the program pages starting on page 31.

Alcohol and Substance Abuse Disorders

Joint Warfighter Medical Research

Military Burn

Neurotoxin Exposure Treatment Parkinson's

Orthotics and Prosthetics Outcomes

Peer Reviewed Alzheimer's

Trauma Clinical Research Repository

Vision

TECHNOLOGICAL ADVANCES (CONT.)

Defense Medical Research and Development Program

Dr. Raymond Goodrich demonstrated that the Mirasol® pathogen reduction technology system is an effective method for reducing blood-borne pathogens in whole blood. The system uses riboflavin (vitamin B2) and ultraviolet-light treatment to disrupt pathogen replication and has potential to reduce the risk of transmission of blood-borne infections.

Dr. Richard Hogle developed and refined the BrainPort vision device for visually impaired individuals. The non-surgical assistive technology delivers electro-tactile signals to an individual's tongue to provide perceptual cues relating to features such as object detection, location, and motion.

Lung Cancer Research Program

Dr. Maximillian Diehn contributed to the development of a non-invasive method, dubbed Cancer Personalized Profiling by Deep Sequencing, for isolating and detecting rare, cancer-associated mutations in circulating DNA from blood to measure disease burden. This technology may be applicable across all cancers.

Ovarian Cancer Research Program

Dr. James Cooper developed universal T-cells for immunotherapy that does not require patient-donated cells for their own therapy; in mouse models, these effectively eliminate implanted human-derived ovarian cancer cells. Concurrently confirming receptor tyrosine kinase-like orphan receptor-1 as an ovarian cancer-specific target for these cells.

Peer Reviewed Medical Research Program

Dr. Roy Bloebaum developed an osseointegrated device that allows direct skeletal attachment of prostheses to amputated limbs. With funding from an FY05 Advanced Technology Award, he and his colleagues at the VA Salt Lake City Health Care System and the University of Utah designed and developed implants for human cadaveric and large-animal models of above-knee amputation, and demonstrated loadbearing ability and lack of infection for up to 12 months in the animal model. An early feasibility study of the implants in humans is now being implemented. The technology offers great promise for individuals with amputations who, due to the nature of their limb loss or other complications, cannot rely on standard prostheses with socket-type attachment systems.

Dr. Ronald Triolo used funding from an FY04 Investigator-Initiated Research Award to develop a prototype hybrid neuromechanical gait assist system that combines electrical stimulation of paralyzed muscles with a controllable hydraulic exoskeleton, and he demonstrated the system's successful ability to assist individuals with lower-extremity motor deficits to perform a variety of activities such as standing, walking, and descending stairs. Dr. Triolo and colleagues are now developing a second-generation, self-contained, portable system to allow for clinical testing outside a laboratory setting.

Peer Reviewed Orthopaedic Research Program

Dr. Joan Sanders developed an in-socket sensor to monitor residual limb volume mass as a diagnostic tool and to act as a feedback control for volume management devices.

Dr. Aaron Dollar developed a body-powered prosthetic hand prototype that allows for a range of grasping positions and the ability to adapt passively to the shape of any object within its grasp.

Dr. Cari Whyne developed a novel implant to improve the 3D reconstruction of complex craniomaxillofacial skeletal fractures.

TECHNOLOGICAL ADVANCES (CONT.)

Dr. Jason Wheeler developed several technologies to benefit amputees, including a prosthetic socket sensor system that can measure pressure at the socket/limb interface, and sockets that can adjust their shape to accommodate volume changes within the residual limb.

Prostate Cancer Research Program

Dr. Neil Bander and colleagues, with multiple PCRP awards beginning in FY97, developed a humanized antibody, J591, that targets prostate-specific membrane antigen and linked it to radioactive isotopes (e.g., Lu177) for treatment and imaging of prostate cancer. Lu177-J591 has been validated for its ability to specifically target prostate cancer in hundreds of prostate cancer patients. Dr. Bander has now linked duocarmicin (duo), a DNA alkylating agent 1,000-fold more potent than doxorubicin, to J591 to complete assembly of a new antibody–drug conjugate that will enable the specific delivery of anti-cancer drugs only to tumor cells that express the target antigen. The J591–duocarmicin conjugate has been found to be highly effective in animal models, especially against castration-resistant prostate cancer.

Psychological Health and Traumatic Brain Injury Research Program

Dr. Corinna Lathan was awarded an Army Rapid Innovation Fund Award to assess the usability of the Defense Automated Neurobehavioural Assessment (DANA) tool in Service Members at various stages of a combat deployment cycle and rapidly transitioned the technology to clinical use. DANA is a computerized cognitive test battery that can assist healthcare professionals in assessing various brain health concerns in a clinical setting. The tool is a phone or tablet app that can be deployed on both iOS and Android operating systems. The company has successfully obtained FDA clearance for the mobile medical application.

Drs. James Tour and ***Thomas Kent*** of the Mission Connect Consortium synthesized potent antioxidant nanomaterials that use small carbon nanotubes to carry antioxidants for the treatment of oxidative stress following TBI, representing an entirely new class of treatment for TBI.

Spinal Cord Injury Research Program

Drs. Gregory Clark and ***Lee Miller*** created a novel brain–machine interface in an animal model by implanting high-count electrode arrays into a peripheral nerve in the animal's forearm that can activate paralyzed muscles in the forearm, wrist, and hand. They have shown long-term (> 6 months) viability and functionality of the implants.

Dr. Molly Shoichet synthesized a bioengineered cell delivery vehicle that is composed of an injectable hydrogel of hyaluronan/methylcellulose covalently modified with platelet-derived growth factor-AA, used the vehicle to deliver neural precursor cells (NPCs) to rats with injured spinal cords, and determined that the NPCs can enhance locomotor function in these animals.

UNDERSTANDING RISK

Autism Research Program

Drs. Alberto Ascherio, Susan Santangelo, and ***Marc Weisskopf*** using the Nurses' Health Study II, identified maternal environmental risk factors before and during pregnancy that may increase the incidence of autism in children of study subjects.

UNDERSTANDING RISK (CONT.)

Breast Cancer Research Program

Dr. David Goldgar and ***Dr. Susan Neuhausen***. Breast and ovarian cancer risk is greater in individuals with mutations in the BRCA1 and BRCA2 genes. The likelihood of BRCA1/BRCA2 mutations is higher in certain populations, including individuals of Ashkenazi Jewish descent. BCRP funding contributed to the discovery of the BRCA2 617delT mutation, one of the three founder BRCA1/BRCA2 mutations that occur in Ashkenazi Jews. The BRCA2 617delT mutation is now part of a commercialized test for BRCA1/BRCA2 gene mutations in this risk group.

Dr. Eldon Jupe. Risk association studies funded by BCRP formed the foundation for a breast cancer risk assessment test. Single-nucleotide polymorphisms (SNPs) are DNA sequence variations that occur when a single nucleotide (A, T, C, or G) in the genome sequence is altered. OncoVue® is the first genetic-based breast cancer risk test that incorporates a woman's SNPs with personal history to estimate her risk for breast cancer. This test can identify high-risk patients and enable clinicians to individualize breast cancer screening and monitoring. OncoVue® is commercially available and is currently offered at several breast care centers in the United States.

Neurofibromatosis Research Program

Dr. Mia MacCollin established associations between types of NF2 mutations and clinical features, and also developed novel methods for detecting NF2 mutations.

Dr. Kathryn North established that MRI T2 hyperintensities measured in children with NF1 are a good predictor of cognitive dysfunction in adulthood.

Dr. William Slattery III characterized the growth rates and clinical course of tumors associated with NF2.

Ovarian Cancer Research Program

Dr. Mary Daly published the first resource book for high-risk women considering prophylactic oophorectomy, *Ovarian Cancer Risk-Reducing Surgery: A Decision-Making Resource*.

Dr. David Bowtell discovered that the Asn372His genotype of BRCA2 significantly increases the risk of ovarian cancer. Additionally, Dr. Bowtell identified differences in epidemiological risk factors between ovarian, fallopian, and primary peritoneal cancer.

Dr. Fergus Couch identified a genetic locus associated with risk of ovarian cancer in BRCA1 mutation carriers, but not in BRCA2 mutation carriers or the general population. His report on this finding was the first published report for a BRCA1-specific risk for ovarian cancer.

Peer Reviewed Cancer Research Program

Dr. Charles Lin created the first comprehensive chromatin and transcriptional map of multiple myeloma in both cell lines and primary patient cells.

Dr. Wenwei Hu studied the link between chronic stress, radiation exposure, and cancer development, showing that chronic stress elevated glucocorticoid levels by inducing SGK1, a negative inhibitor of p53, and promoting tumorigenesis.

Drs. Eva Hernando and ***Iman Osman*** performed microRNA analysis of human melanoma and found that high expression of miR-30b/30d correlated with metastatic potential and shorter time to recurrence, as well as with reduced overall survival.

UNDERSTANDING RISK (CONT.)

Peer Reviewed Medical Research Program

Dr. Curtis Harris of the National Cancer Institute developed a prognostic classifier based on expression levels of four genes, BRCA1, HIF1A, DLC1, and XPO1, in Stage I lung adenocarcinoma. Dr. Curtis validated the 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.

Tuberous Sclerosis Complex Research Program

Steven Sparagana developed a clinical database that documents the natural history and variability of Tuberous Sclerosis Complex (TSC). The database is currently managed by TS Alliance; 1,187 people are enrolled as of March 2013.

LANDMARKS IN BASIC SCIENCE

Autism Research Program

Dr. Eric Klann showed that increased EIF4E gene expression in mice results in aberrant behaviors reminiscent of autism.

Breast Cancer Research Program

Dr. Michael Wigler. BCRP funding contributed to the original discovery of the tumor-suppressor gene phosphatase and tensin homolog (PTEN). In normal cells, PTEN functions as a tumor-suppressor protein that helps regulate cell division and growth. PTEN is one of the most frequently mutated genes in several cancers, and PTEN mutations have been shown to be predictive of aggressive cancer. PTEN mutations also occur in a group of genetic syndromes that are characterized by malignant and benign tumors. A PTEN test is commercially available to confirm PTEN mutations for clinical and prenatal diagnoses, and identification of at-risk family members.

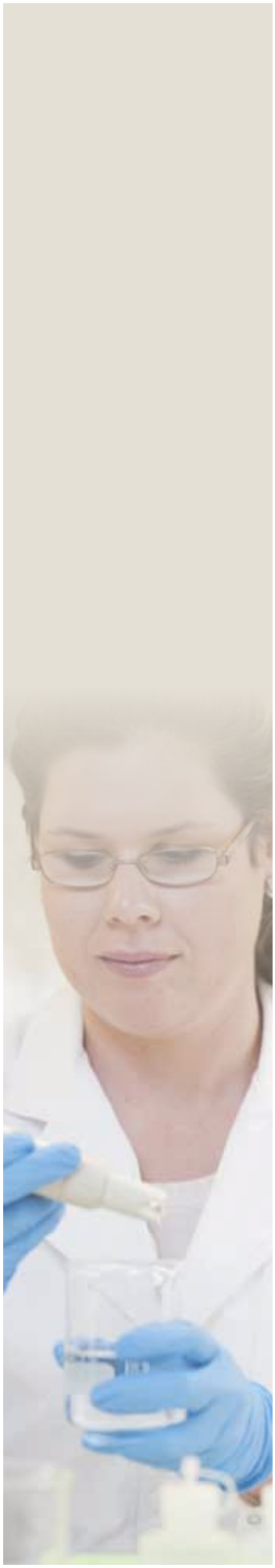
Dr. Bing Xia. BCRP funding contributed to the discovery of PALB2, a BRCA2 binding protein. PALB2 and BRCA2 work together to mend broken strands of DNA, which helps to maintain the rate of cell growth. While BRCA1 and BRCA2 gene mutations are high-risk factors for breast cancer, these mutations do not account for all familial breast cancers. Identification of mutations in the PALB2 gene indicates an approximate twofold increase in breast cancer susceptibility due to its inability to interact with BRCA2. A commercialized PALB2 genetic test is available for those with familial breast cancer.

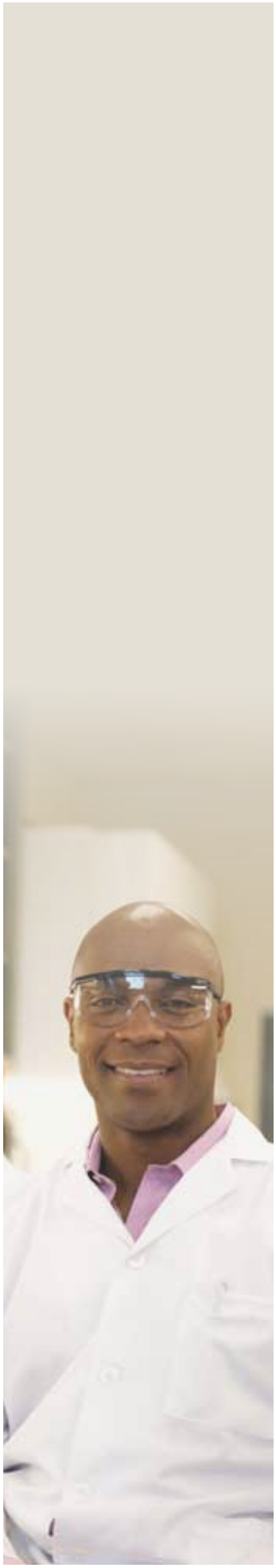
Bone Marrow Failure Research Program

Dr. Omar Abdel-Wahab showed that deletion of Asxl1, a protein co-factor important in epigenetic regulation of gene transcription, resulted in hallmark features of myelodysplastic disorders, thus creating a disease-relevant genetically accurate model of myelodysplastic disorders.

Lung Cancer Research Program

Dr. Hannah Rabinowich established a novel mechanism of cross-regulation between autophagy and apoptosis via the Atg7/caspase-9 complex as a way lung cancer cells can develop drug resistance to epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors.





LANDMARKS IN BASIC SCIENCE (CONT.)

Neurofibromatosis Research Program

Dr. Allan Belzberg developed the tibial neuroma transposition animal model of neuroma pain and hyperalgesia associated with neuropathic pain.

Dr. Duojia Pan determined that the Merlin/NF2 tumor suppressor functions through the YAP oncoprotein to regulate mammalian tissue growth.

Dr. Karen Cichowski identified a negative-feedback signaling pathway that protects benign lesions from becoming malignant in patients with NF, and established that different mechanisms of NF1 inactivation occur in different tumors, which may result in changes in the tumor response to specific therapies.

Dr. Karen Cichowski demonstrated that neurofibromin regulates the mTOR pathway through activated Ras.

Dr. Andrea McClatchey provided insight into the function of the NF2 (merlin) protein, which acts as a tumor and metastasis suppressor by controlling cell–cell contact.

Dr. Margaret Wallace identified that the loss of neurofibromin is associated with tumorigenesis.

Dr. Luis Parada characterized loss of NF1 in various cell types and demonstrated that loss of NF1 in the Schwann cell lineage was sufficient to generate tumors.

Dr. Peleg Horowitz identified a mutation in the proto-oncogene CBL and a genomic translocation disrupting retinoblastoma protein in human schwannoma samples.

Dr. Morvarid Mohseni identified several potential therapeutic downstream targets for NF2-mediated Yap1 activation.

Dr. Wei Mo showed that CXCR4/CXCL12 mediates the cell-cycle progression in NF1-associated MPNST.

Dr. Marlan Hansen demonstrated that the ErbB2 signaling pathway is essential for vestibular schwannoma growth and an attractive therapeutic target.

Dr. Robert Martuza developed a herpes simplex virus vector therapy for NF2 that reduces schwannoma tumor volume in an NF2 mouse model.

Dr. Raymond Mattingly demonstrated that a novel farnesyltransferase inhibitor combined with lovastatin reduces proliferation and induces apoptosis of MPNST cells, and is a potential treatment for NF1.

Dr. Margaret Wallace demonstrated that steroid hormones can significantly affect the growth of NF1 tumor cells.

Peer Reviewed Cancer Research Program

Dr. Bruce Robinson showed that targeted removal of Treg can significantly enhance anti-tumor immunity, thus delaying tumor development in a mesothelioma mouse model.

Dr. Muneesh Tewari and ***Dr. Allan Pantuck*** optimized a detection method for miRNA-210 and demonstrated that miRNA-210 was elevated in renal carcinoma serum samples.

Peer Reviewed Medical Research Program

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 cystogenesis, identifying Integrin beta 1 as an essential mediator of cyst formation and a potential target for the first therapeutic to treat ADPKD.

Peer Reviewed Orthopaedic Research Program

Dr. Sameer Shah developed a device to gradually lengthen an intact proximal stump of an injured nerve toward the distal stump, leading to rapid reconnection in a rat sciatic nerve model.

Prostate Cancer Research Program

Dr. Evan Keller demonstrated that blocking the activity of RANKL slows the progression of prostate cancer growth in bone. The monoclonal antibody against RANKL, denosumab, was later synthesized and, in 2010, attained FDA approval as XGEVA, becoming the standard of care for the treatment of bone-related events in advanced prostate cancer.

Spinal Cord Injury Research Program

Dr. Douglas Smith developed a spinal cord repair technique using tissue-engineered nerve grafts (TENGs)—the first-ever living engineered nervous tissue based on the naturally occurring process of "stretch growth of axon tracts." He observed nerve regeneration across TENGs as far as 6 weeks post-transplantation in a 5-millimeter full transection SCI rat model. There is also evidence of host (rat) axon integration with, and along, the TENG axons, which may lead to the reconnection of impaired neural networks in these animals.

Dr. Radi Masri discovered a novel brain circuit that can be manipulated to manage pain following SCI. He found that stimulation of the motor cortex reduces pain by activating neurons in the zona incerta (an inhibitory nucleus in the brain).

Dr. Diane Snow developed a recombinant enzyme, ADAMTS-4, that can naturally degrade chondroitin sulfate proteoglycans, which inhibit neural regeneration. She showed that ADAMTS-4 can promote neural regeneration and ameliorate some of the negative consequences of SCI injury in a rodent model.

Dr. Victor Arvanian developed a viral vector-based construct expressing an antibody to NG-2, which is an inhibitory chondroitin sulfate proteoglycan. He found that co-administration of the NG-2 construct with a viral vector expressing neurotrophin-3 in adult rat spinal cord following contusion SCI leads to improved locomotor function and improved spinal circuitry transmission in these animals, which suggests that this regimen could be developed into a gene therapy for individuals with SCI.

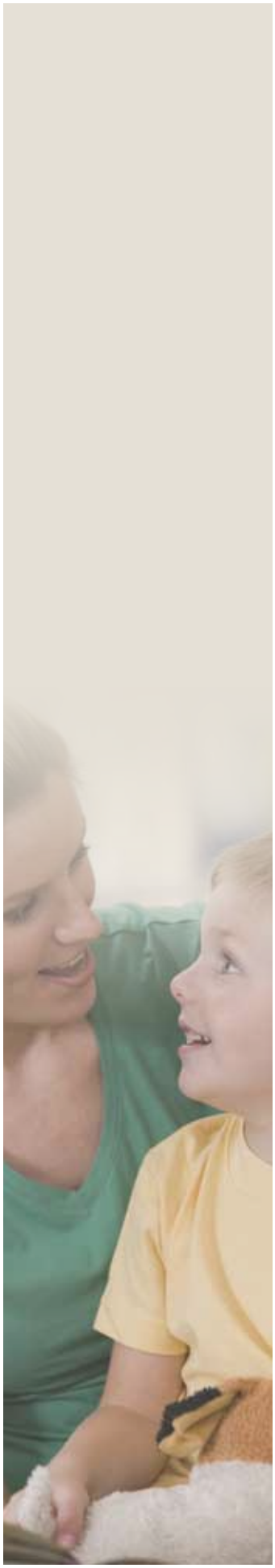
Dr. Adina Michael-Titus demonstrated in both mouse and rat contusion models of SCI that animals treated with docosahexaenoic acid (DHA; an omega-3 fatty acid) 30 minutes post-injury show improved locomotor function that is correlated with increased neuronal survival in the injured spinal cord. Improved locomotion is associated with increased numbers of microglia and macrophages in the rat model, suggesting an increase in inflammation in the DHA-treated injured spinal cord.

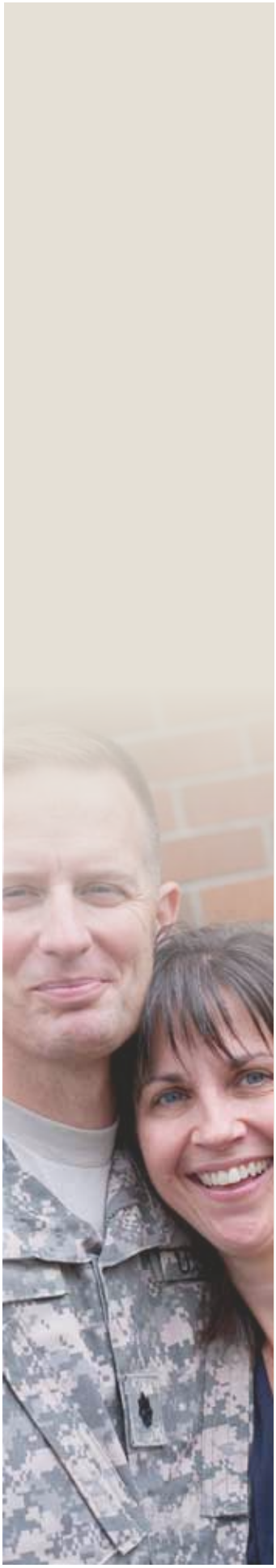
Dr. Carl Creutz, using an in vitro assay involving synthetic membrane vesicles, determined that human calcium-dependent, membrane-binding proteins of the annexin or copine classes are effective at preventing damage and repairing damage to lipid membranes caused by osmotic shock or other chemical or physical stresses, which suggests that these proteins may be able to protect or promote the repair of cell membranes following SCI.

Tuberous Sclerosis Complex Research Program

Dr. Jane Yu found that 17-beta estradiol increases cyclooxygenase-2 (COX-2) activity in TSC-null cells and that treatment with a COX-2 inhibitor decreases cell proliferation and tumor growth in vitro and in vivo.

Dr. Teresa Wood determined that TSC is a critical upstream regulator of mTORC1 and mTORC2 in oligodendrocyte lineage cells.





LANDMARKS IN BASIC SCIENCE (CONT.)

Dr. Thomas Darling showed that tranilast, an antiallergic and antifibrotic drug, has selective inhibitory effects on the viability of TSC skin tumor cells, indicating that it may be useful as an adjunctive agent for the treatment of TSC.

Dr. Aristotelis Astrinidis determined the mechanism by which PLK1 (polo-like kinase 1) interacts with TSC1 and demonstrated that PLK1 inhibitors represent a potential treatment avenue for individuals with TSC.

Dr. Kun-Liang Guan identified multiple regulators of the mTORC1 pathway and showed that cAMP elevation inhibits TORC1.

Dr. Vera Krymskaya identified that a complex formed between TSC1 and TSC2 regulates cell adhesion and motility and that dysregulation of the complex formation may contribute to the pathogenesis of TSC.

Dr. Elizabeth Henske demonstrated that hamartin and tuberin play critical roles in amino acid sensing, uptake, and metabolism, and that TSC symptoms may be linked to defects in those key cellular functions.

Dr. Brendan Manning demonstrated that rapamycin treatment in combination with low-dose tunicamycin results in a cytotoxic response in TSC null cells.

Dr. Bernardo Sabatini conducted studies that show that the TSC pathway regulates neuron soma size, the density and size of dendritic spines, and the properties of excitatory synapses in hippocampal pyramidal neurons in both cell culture and animal models.

SHIFTING PARADIGMS

Autism Research Program

Dr. Armin Alaedini used samples from a cohort of well-characterized patients diagnosed with autism, their unaffected siblings, and unrelated controls to find that patients with autism had immunoglobulin G antibodies to gluten linked to gastrointestinal symptoms that were different from those of celiac disease.

Breast Cancer Research Program

Dr. Kathryn Verbanac and ***Dr. Douglas Reintgen***. The previous standard for detecting breast cancer invasion into the lymph nodes was to remove the majority of axillary lymph nodes and search for cancer cells. In a significant proportion of women, this causes lymphedema of the arm, a condition that compromises functionality and quality of life. In sentinel lymph node biopsy, lymph node removal is limited to only the first few nodes that receive lymph drainage from the breast. This diagnostic/prognostic technique enables clinicians to determine tumor staging and if more-extensive lymph node surgery is necessary. BCRP provided funding for multicenter clinical trials that validated lymph node mapping and sentinel lymph node biopsy as an accurate method to predict the presence of disease in the axillary lymph nodes.

Bone Marrow Failure Research Program

Dr. Charles Lin demonstrated the critical role of regulatory T cells in maintaining immune-privilege mechanisms of the hematopoietic stem/progenitor cells (HSPC) niche. This work has established a novel concept of immune privilege in the HSPC niche and uncovered its molecular and cellular mechanisms.

Neurofibromatosis Research Program

Dr. David Gutmann developed a non-invasive technique to detect optic glioma in a mouse model of NF1.

SHIFTING PARADIGMS (CONT.)

Ovarian Cancer Research Program

Dr. Gillian Mitchell and ***Dr. David Bowtell*** identified BRCA1/2 mutations in 14% of the 1,001 samples from women with invasive nonmucinous ovarian tumors. Moreover, they observed that a high proportion of women carrying BRCA1/2 mutations did not have a significant family history of breast or ovarian cancer, thereby challenging the current practice of offering genetic testing only to women with a positive family history for those two cancers.

ENHANCING HEALTHCARE

Amyotrophic Lateral Sclerosis Research Program

Dr. Pierre Drapeau, using a large drug screen to identify chemical modifiers of TDP-43, successfully identified a number of neuroleptic compounds that restored mobility in model systems, including the antipsychotic drug pimozide. Using the data from these studies, Dr. Drapeau initiated a collaboration to begin a Stage IIb randomized clinical trial to look at the effects of pimozide in patients with amyotrophic lateral sclerosis (ALS).

Autism Research Program

Dr. Daniel Cox developed a virtual-reality driver simulator to train and evaluate driving skill in teens with ASD.

Breast Cancer Research Program

Dr. Dennis Slamon. Herceptin® (trastuzumab) is a monoclonal antibody that targets the human epidermal growth factor receptor 2 (HER2). HER2+ breast cancer accounts for approximately 25% of all breast cancers. BCRP was instrumental in supporting the preliminary in vitro and in vivo studies needed to test the efficacy of Herceptin, which later led to clinical trials and commercialization. Herceptin revolutionized breast cancer treatment and the field of targeted therapeutics. Herceptin is part of standard-of-care treatment regimens for HER2+ early-stage and metastatic breast cancers.

Defense Medical Research and Development Program

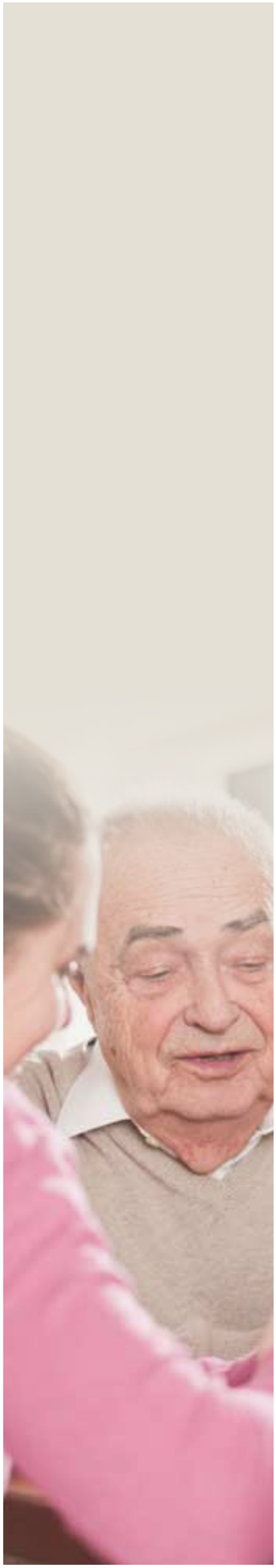
Dr. Kenton Kaufman developed a specialized treadmill training program to increase mobility and reduce the risk of falls among individuals with lower-extremity limb amputations. Early findings include improvements in gait and stability among trainees.

Gulf War Illness Research Program

Dr. James Baraniuk discovered unique alterations in brain structure and function in GWI-affected veterans. Dr. Baranuik used fMRI to examine the effects of exercise on working memory in GWI patients. He found that the GWI patients, following exercise, had significant white matter dysfunction compared to controls. Additionally, distinct cognitive responses, including central perceptual, and energy efficiency were identified in the GWI patient compared to controls. These responses could be further categorized into distinct GWI-related subtypes. These findings point to an inability to recruit cognitive recourses during exercise-induced fatigue and are an indication that the heterogeneous GWI can be subdivided for more-targeted treatment.

Neurofibromatosis Research Program

Dr. Bruce Korf. The NF Clinical Trials Consortium was established in 2006 and expanded in 2011 to include clinical trials for NF2.



ENHANCING HEALTHCARE (CONT.)

Dr. Nancy Ratner provided evidence supporting clinical trials of MEK inhibitors for NF1 malignant peripheral nerve sheath tumors.

Dr. Victor-Felix Mautner demonstrated that imatinib mesylate (Gleevec) inhibits Schwann cell viability and reduces the size of plexiform neurofibromas in a xenograft model, and reduces tumor volume of plexiform neurofibroma fragments obtained from NF1 patients, providing preliminary data for clinical trials.

Dr. Alcino Silva demonstrated that lovastatin treatment reverses learning deficits in an NF1 mouse model.

Dr. Karen Stephens used MRI to detect shwannomas in a transgenic mouse model of NF2.

Dr. Bruce Korf studied the natural history of NF1 plexiform neurofibromas and established volumetric MRI as the standard approach for measuring these tumors in clinical trials.

Dr. William Slattery III established a consortium of nine international sites to study the natural history of NF2 and developed standard operating procedures for MRIs and an NF2-specific database.

Ovarian Cancer Research Program

Dr. Zhen Zhang, in collaboration with Vermillion, Inc., developed OVA1™, the first in vitro diagnostic multivariate index assay of proteomic biomarkers cleared by FDA to help physicians identify ovarian cancer patients whose surgeries should be referred to a gynecologic oncologist.

Drs. David Bowtell and ***Gillian Mitchell*** found that 44% of the 141 women with nonmucinous ovarian tumors carrying BRCA1/2 mutations did not have a family history of ovarian cancer or breast cancer. This resulted in Australia changing the genetic testing guidelines in 2013 to include all women diagnosed with non-mucinous ovarian cancer under the age of 70.

Dr. Robert Kurman's consortium developed and validated an inclusive scoring algorithm to assist pathologists in diagnosing Spatiotemporal Image Correlation Spectroscopy, the proposed precursor for most ovarian high-grade serous cancers.

Dr. Tomas Walsh confirmed that a loss-of-function mutation in RAD51D gene predisposes women without BRCA1/2 mutations to ovarian cancer but not to breast cancer. This information guides genetic testing kits for women in families with ovarian cancer with or without breast cancer.

Peer Reviewed Cancer Research Program

Drs. Richard Gilbertson, David Malkin, Rodney Guy, and ***David Ellison*** defined the molecular landscape for choroid plexus carcinoma, a rare type of pediatric brain tumor with a high mortality rate. Identification of gene alterations assisted in the search for different drugs and led to a screen of over 1.2M compounds. Gemcitabine was identified as a candidate treatment and is progressing toward clinical trials.

Dr. Mansour Mohamadzadeh found that an lipoteichoic acid (LTA)-deficient *Lactobacillus acidophilus* regulates inflammation and protects against colonic polyposis in a murine model. This discovery may lead to an oral therapeutic to prevent the initiation of colorectal cancer.

Dr. David Yu identified CHD7 as a novel biomarker candidate for predicting gemcitabine response in early-stage resected pancreatic ductal adenocarcinoma patients, and he discovered that low CHD5 expression predicts poor outcomes in resected pancreatic cancer patients.

Peer Reviewed Medical Research Program

Dr. Barbara Soller, with funding from an FY02 Investigator-Initiated Research Award, developed CareGuide™, a portable, fiber optic, near-infrared spectroscopic sensor system that noninvasively measures muscle pH, oxygen, and hematocrit. Dr. Soller and collaborators at the U.S. Army Institute of Surgical Research tested the system in a lower-body negative pressure model of progressive hemorrhagic shock and demonstrated that muscle oxygen levels may be an early indicator of blood loss. The CareGuide™ has received FDA clearance, and a ruggedized version for use on military aircraft is now in development.

Dr. Stephen Savarino, with support from an FY03 New Program Project Award, showed that bovine milk immunoglobulin (BIgG) collected from cows immunized with enterotoxigenic *Escherichia coli* (ETEC) antigens and administered orally provided protection against ETEC challenge (traveler's diarrhea) in humans. Based on the success of this study, he and his colleagues are now using the same approach to develop orally administered BIgG against an additional strain of ETEC, with the goal of developing a multivalent, food-based antidiarrheal supplement that will confer protection against the predominant cause of infectious diarrhea in deployed Warfighters.

Prostate Cancer Research Program

Dr. David Jaffray and colleagues developed cone-beam computed tomography with a flat-panel imager that revolutionizes image-guided radiotherapy, enabling radiologists to image exact tumor location and then direct curative radiation doses to the prostate. The cone-beam computed tomography imaging approach has proven to be a substantial commercial success, with over 80% of radiation machines sold today equipped with it.

Psychological Health and Traumatic Brain Injury Research Program

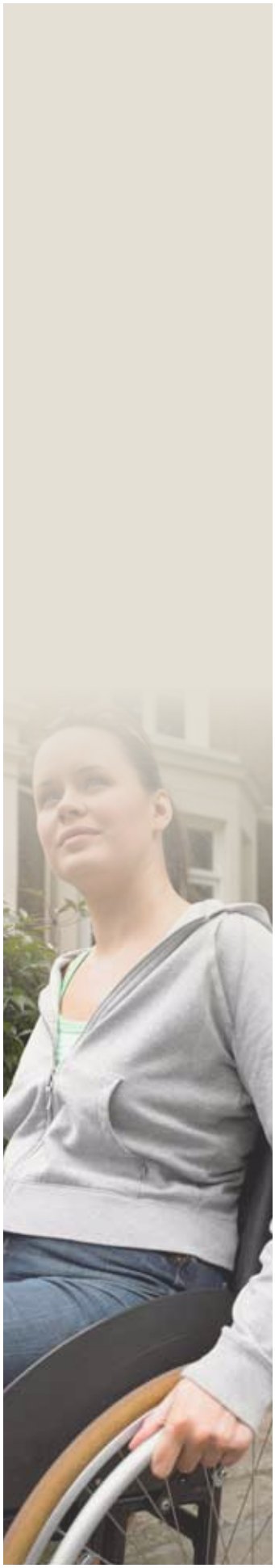
Dr. Murray Raskind successfully completed a double-blind randomized controlled trial to evaluate Prazosin efficacy and tolerability to treat nightmares and sleep disturbances related to combat trauma PTSD in active-duty Service Members. The study demonstrated that Prazosin was well tolerated and highly effective in reducing PTSD symptoms, including sleep-related comorbidities. Prazosin is an inexpensive, clinically available drug, and this study supports immediate translating of the findings to support clinical application.

Spinal Cord Injury Research Program

Dr. Leslie Morse conducted a clinical trial to determine the ability of functional electrical stimulation–rowing combined with zoledronic acid (slows bone loss) to reverse bone deterioration due to SCI. Early results indicate increased bone volume and stiffness in the lower extremities of people with SCI in response to rowing.

Drs. Damien Pearse, Mary Bunge, and ***James Guest*** conducted dosage, safety, and toxicity studies of human Schwann cell implantation in animal models of SCI. They observed a significant improvement in locomotor function in animals treated with human Schwann cells versus injured controls. Results of this study have led to a Phase I clinical trial to evaluate safety in individuals with subacute SCI.

Dr. Linda Noble determined that a matrix metalloproteinase inhibitor given 8 hours after a relatively severe SCI in mice results in improved neurological outcome and bladder function by 6 weeks. If preclinical studies in a larger-animal model show similar results, this compound could be quickly transitioned into human clinical trials.



ENHANCING HEALTHCARE (CONT.)

Drs. Gregory Dekaban and ***Arthur Brown*** developed a monoclonal antibody against the CD11d subunit of the β2 integrin family that prevents the infiltration of inflammatory cells into an injured spinal cord and improves locomotor recovery in spinal cord-injured mice and rats. Eli Lilly and Co. is now developing a humanized version of the mouse and rat CD11d antibody at a cost of $3.74M.

Dr. Danuta Radzioch demonstrated that the drug fenretinide can improve locomotor recovery in mice with SCI when administered soon after injury, presumably by correcting the deregulation of fatty acids that causes inflammation post-injury. Preliminary blood plasma analysis of 7 SCI and 12 spinal fracture patients supports the hypothesis of a lipid imbalance after a traumatic SCI.

Dr. Weiping Qin discovered in a preclinical rat model of SCI that the anabolic steroid nandrolone reduces bone loss after SCI and that the potential mechanism involves the activation of Wtn pathway signaling.

Dr. Candace Floyd, using a rat model of SCI, observed that the antidepressant venlafaxine, when administered in conjunction with exercise rehabilitation, negates the functional gains resulting from rehabilitation, but does not have any effect on the baseline functional levels in the animals.

Dr. John Redell determined that daily administration of a low dose of valproic acid leads to a rapid, sustained, and significant improvement in Basso, Beattie, and Bresnahan locomotor behavioral assessment scores, and to a significant decrease in total synaptophysin levels in SCI animals relative to saline-treated controls.

Tuberous Sclerosis Complex Research Program

Dr. Mary Kay Koenig led a randomized trial of the safety and efficacy of a topically applied formulation of rapamycin to treat cutaneous angiofibromas in individuals with TSC.

Dr. Charles Nelson determined a difference in face-processing and electroencephalography frequencies in children that may to lead to early diagnostic criteria for autism in children with TSC.

RESEARCH RESOURCES

Breast Cancer Research Program

Dr. Gregory Hannon and ***Dr. Stephen Elledge***. RNA interference (RNAi) is a cellular system that controls which genes are active or silent. The selective effect of RNAi on specific gene expression makes it a valuable research tool. Small hairpin RNAs (shRNAs) are one of the gene-silencing mechanisms of RNAi. BCRP supported the development of whole-genome shRNA libraries that target more than 30,000 genes. This commercially available research tool (Expression Arrest™) provides researchers with ready-to-use, rapid RNAi screens for the entire human and mouse genomes to study gene regulation and identify new therapeutic targets in many diseases and conditions, including cancer.

Dr. Mary Daly. BCRP supported the establishment of a high-risk breast cancer registry to gather genetic and environmental risk information about women with familial breast cancer. This registry evolved into the Margaret Dyson Family Risk Assessment Program for individuals at risk for breast or ovarian cancers. This program, which serves Philadelphia and its surrounding communities, provides a range of risk assessment, screening, and preventive services to individuals who have a family history of breast or ovarian cancer.

Lung Cancer Research Program

Dr. Christopher Moskaluk. LCRP provided support to create the first national early-lung cancer biospecimen repository that contains tissues and biological fluid samples linked to clinical and outcome data. This resource is available to all biomedical researchers and aims to assist clinical investigators in the study of lung cancer genetics, novel diagnostic and prognostic tests for cancer, and candidate biomarkers.

Neurofibromatosis Research Program

Dr. Jeremie Vitte developed a mouse model of schwannomatosis-related neuropathic pain.

Dr. Feng-Chun Yang demonstrated that growth factor TGF-beta secreted from mast cells plays a critical role in initiation and progression of neurofibromas, and she developed a mouse model of NF1 that displays skeletal manifestations similar to those of humans with NF1.

Dr. Kevin Shannon developed mouse models of MPNSTs, PMF, astrocytomas, and ependyomas for assessing the mutagenic potential of NF1 tumor therapies.

Dr. Tyler Jacks developed the first mouse model of NF1-related MPNSTs.

Ovarian Cancer Research Program

Dr. Brad Nelson developed a new bioinformatics program for assembling high-throughput sequence data and querying for the presence of single-nucleotide variants in ovarian cancer.

Dr. Patricia Shaw established the Toronto Ovarian Cancer Research Network, a repository of prophylactic surgery specimens from BRCA mutation carriers with a database of BRCA mutation-carrier and control-group gene expression signatures.

Dr. Denise Connolly developed the mouse model of ovarian leiomyosarcomas.

Dr. Igor Jurisica developed online databases (OPHID/I2D) of known and predicted protein–protein interactions (PPI), as well as the software package (NAViGaTOR) for visualizing and analyzing PPI networks.

Peer Reviewed Orthopaedic Research Program

Dr. Warren Haggard developed a device to allow simultaneous growth of tendon and bone cells in culture under different strain conditions while on the same scaffold.

Peer Reviewed Medical Research Program

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 the model.

Prostate Cancer Research Program

Dr. Bruce Trock and team. The Prostate Cancer Biorepository Network (PCBN) was initiated in 2010 as a pilot collaborative project between Johns Hopkins University and New York University to deliver high-quality biospecimens for wide usage by the research community. By 2013, the PCBN had accrued over 3,000 specimens prospectively. A number of manuscripts have been published in high-impact journals such as *Proceedings of the National Academy of Sciences, Cancer Research, Oncogene,* and *Journal of Clinical Investigation* using samples obtained from the PCBN. In response to the FY13 Prostate Cancer Pathology Resource Network Award Program Announcement, the existing PCBN has been expanded with the addition of new sites in 2014.

Psychological Health and Traumatic Brain Injury Research Program

Dr. Michael McCrea. The Military Acute Concussion Evaluation (MACE) is a widely used standardized method for acutely evaluating cognitive dysfunction-related mTBI in military personnel. This study examined use of the MACE between 2006 and 2009 for reliability, validity, and clinical utility. The study found the instrument to be reliable and valid for measuring cognitive function following military-related mTBI, and that MACE is a valuable tool to rapidly assist in clinical decision-making following mTBI.

Drs. Emmy Miller, Cynthia Harrison-Felix, and ***Claudia Robertson*** were funded with different awards in FY13 to expand data-sharing resources for TBI. The Federal Interagency TBI Research (FITBIR) informatics system is a joint DoD- and NIH-developed platform for sharing data generated from funded TBI studies; it facilitates and enhances collaboration and supports the National Research Action Plan. New awards as of the FY11 funding cycle are required to submit data to FITBIR. These investigators have received new awards from FY13 funds to support entry of data from completed PH-TBI efforts from prior funding cycles into FITBIR. Access to these "legacy" data will greatly enhance the immediate utility of FITBIR.

Spinal Cord Injury Research Program

Drs. Michael Beattie, Geoffrey Manley, and ***Graham Creasey*** used information from current clinical practice to guide the development of an animal model of SCI plus mild-complicated and moderate TBI. Data derived from the animal model are being used to propose improved guidelines for clinical treatment. This partnership has led to the establishment of a community of practice and research that promotes clinical and basic scientific interaction on the problem of combined brain injury and SCI.

Dr. Mark Tuszynski developed a model of severe SCI in rats that may allow for a more rapid and cost-effective screening of potential therapies for SCI than screening in human trials.

Tuberous Sclerosis Complex Research Program

Dr. Stephen Hammes generated a mouse model that develops uterine leiomyomas and lymphangioleiomyomatosis (LAM)-like smooth-muscle tumors.

Dr. Mark Zervas generated TSC-like symptoms in mice and showed that the timing of TSC1 deletion in neurons in the developing thalamus impacted the extent of the disease in the brain, the degree of abnormality, and the severity of TSC-like symptoms.

Dr. Angelique Bordey developed a mouse model to study the embryonic development of cortical tuber lesions and showed that upregulation of Hif1a transcriptional activity in newborn neurons promotes the growth and persistance of TSC lesions.

Dr. Tin Tin Su developed a quantitative *Drosophila*-based assay to screen compounds and test their ability to rescue the larval lethality of TSC1 homozygous mutants.

Our Programs

The 25 research programs managed or executed share many common features, yet each program is unique and emphasizes the specific needs of the research and advocacy communities. Highlights of these programs are detailed on the following pages.

Alcohol and Substance Abuse Research Program

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

Program History

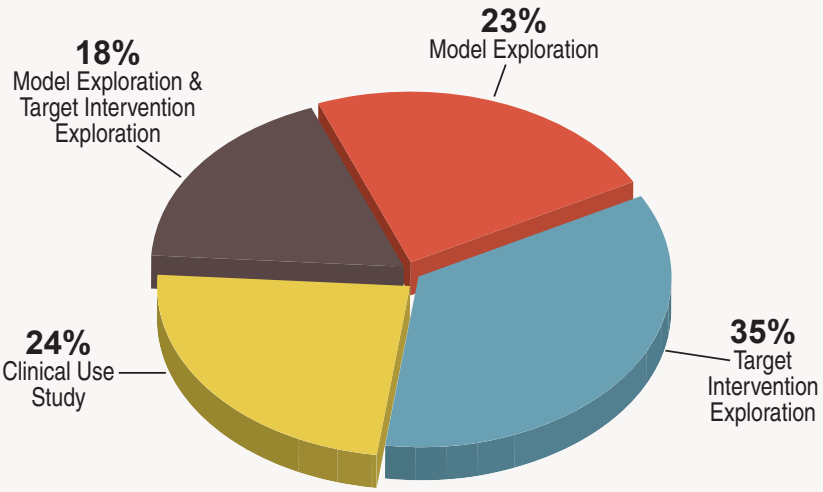
The problem of alcohol and substance abuse is a growing concern among the general public and military personnel and veterans alike. Impacts include reduced levels of readiness, increased crime, mental health problems, and suicides. Post-traumatic stress disorder and other psychological health problems are strongly linked to substance use disorders (SUDs). The Alcohol and Substance Abuse Research Program (ASARP) 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 SUDs, and federal funding for its research has led to a total appropriation of $20.075M to the ASARP.

The goal of the program is to identify and develop new medications to improve treatment outcomes for ASUD, especially related to traumatic brain injury (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.

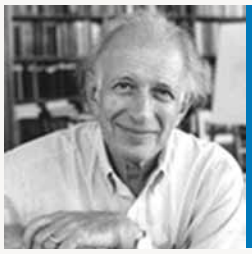
SUDs present a significant cost to the military and complicate the treatment of PTSD and related conditions. Successful identification of medications to treat SUDs, alone or together with psychological or neurological conditions, would decrease costs to the military and facilitate redeployment and increased readiness. Such medications also promise to improve public health and avoid significant social costs outside the military context. The ASARP hopes these new medication-based therapeutic protocols will be helpful for treating those with SUDs.

FY10–FY13 ASARP Research Portfolio*

Total number of awarded projects: 17
Total number of active projects: 8



**Analysis by number of awards.*



ERIC R. KANDEL, M.D., NOBEL LAUREATE, COLUMBIA UNIVERSITY

A Translational Epidemiological Approach to the Molecular Basis of PTSD and Substance Abuse Comorbidity

The major goal of this project was to identify casual molecular mechanisms that underlie important observations in the epidemiology of PTSD and its comorbidity with substance abuse, which may lead to the development of new approaches for preventive screening, diagnosis, and pharmacological intervention into PTSD and the cycle that couples it with drug abuse.

Dr. Kandel's research team has established TIA-1-deficient mice as a novel G x E model for stress vulnerability that will provide new insights into the biology of PTSD. Their analysis of the epidemiological data from the RTI International study has identified several important predictors of PTSD in a large, active-duty military population, including the finding that age, physical and sexual abuse, work and family stress, problem alcohol use and non-medical use of prescription drugs, combat exposure, and rank are important predictors of possible PTSD. Their second epidemiological analysis identified gender-specific differences in PTSD symptoms. Women express more symptom distress than men across all the individual PTSD symptoms, except for hypervigilance, which is more common among men. Their studies raise the possibility that modulating the activity of TIA-1 or changing the expression ration of glucocorticoid receptor isoforms may have therapeutic benefit.

JACQUELINE F. MCGINTY, Ph.D., MEDICAL UNIVERSITY OF SOUTH CAROLINA

Endogenous Modulators Suppress Substance Abuse Disorders Associated with Chronic Stress

The major goal of this project was to focus on intervention with systemic oxytocin (OT) and the long-acting OT receptor agonist, carbetocin, during withdrawal from meth self-administration to suppress exacerbated drug-seeking and accompanying deleterious neuroadaptations in rats with previous exposure to traumatic, inescapable footshock. The potential value of the project is that the suppressive effects of OT on stress-induced exacerbation of drug abuse vulnerability are robust and strengthen the hypothesis that OT may be a novel therapeutic treatment strategy for concurrent SUD with prior traumatic stress exposure in active soldiers and veterans.

Dr. McGinty's research team showed that daily exposure to trimethylthiazonline resulted in a significant elevation of cortisol levels compared to control animals analyzed by ELISA. Data indicate that OT is a promising therapeutic target with potential to positively impact both traumatic stress and SUD vulnerability.

LORI A. KNACKSTEDT, Ph.D., UNIVERSITY OF FLORIDA

Development of an Animal Model and Novel Treatments for Co-morbid PTSD and Cocaine Addiction

The present proposal is unique in that it combines an animal model of PTSD with animal models of cocaine addiction to study the interaction between these two disorders, determine neurobiological changes in animals with co-morbid PTSD and cocaine addiction, and screen potentially translational compounds for their ability to reduce both cocaine intake and PTSD symptoms.

This project is still in the early stages of research, but the researchers have run one cohort of animals through the PTSD induction, assessment, and cocaine self-administration portion of the experiment. They have determined that animals classified as having a PTSD phenotype are more likely to self-administer cocaine initially, thus establishing an animal model of co-morbid PTSD and cocaine addiction.

HOWARD L. FIELDS, M.D., Ph.D., ERNEST GALLO CLINIC AND RESEARCH CENTER

Translational Coordinating Core

The major goal of this core facility is to accelerate the development of new treatments for alcohol and substance abuse and co-morbid conditions. The Institute for Molecular Neuroscience (IMN) Translational Coordinating Core will guide, direct, and accelerate the exploitation of the discoveries of the IMN Consortium by identifying the most promising pharmacological targets, validating their usefulness for alcohol and substance abuse disorders treatment and, in certain cases, performing Phase II proof-of-principle human studies.

Please note that these are only four of many sub-projects funded under the Institute for Molecular Neuroscience Consortium.

Amyotrophic Lateral Sclerosis Research Program

VISION
Improve treatment and find a cure for ALS

MISSION
Fund innovative pre-clinical research to develop new treatments for ALS

Tim Heiser, ALSRP Consumer Reviewer

"I never thought I would hear those three letters. As a consumer reviewer, I found my opinions were highly valued by the scientific reviewers, who truly listened and took my opinions into account when critiquing the research applications. I am optimistic and hopeful that the research funded through the ALSRP will someday lead to a cure."

Program History

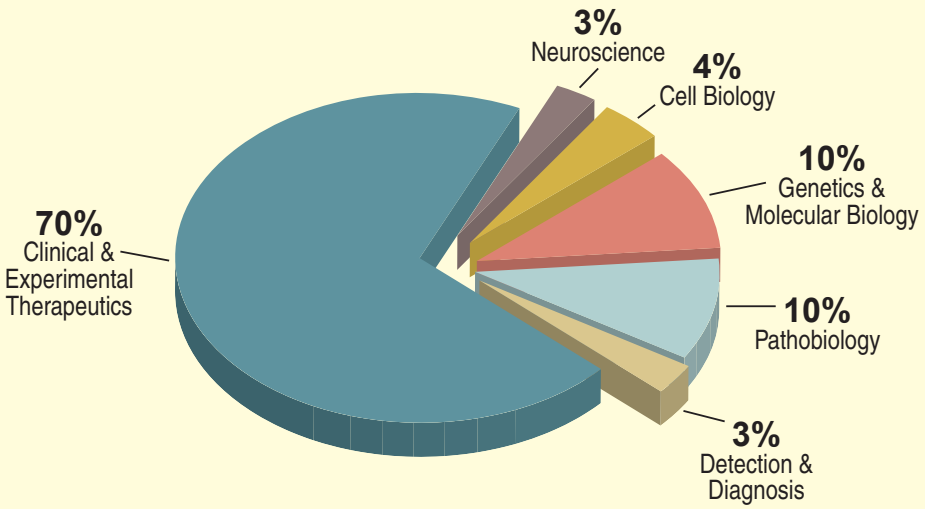
Amyotrophic Lateral Sclerosis (ALS), also known as "Lou Gehrig's Disease," is an incurable, degenerative neurological disorder. For reasons that are not understood, the nerve cells of the brain and spinal cord that control voluntary muscle movement gradually deteriorate. ALS can prove difficult to diagnose because the initial symptoms are both subtle and vague, and can be attributed to a number of conditions. Average life expectancy after diagnosis ranges from 2 to 5 years; about 10% of patients with ALS live more than 10 years after diagnosis. Men and women who have served in the U.S. military are 60% more likely than civilians to develop a fatal muscle-wasting disease such as ALS. In addition, veterans of the 1990-1991 Gulf War have been shown to be twice as likely to develop ALS as the general population, though the reasons for this incidence are not well understood.*

There are currently no known therapies to effectively halt the progression of ALS; however, one FDA-approved drug, riluzole, modestly slows ALS progression. Several drug candidates are now in clinical trials, and some show early promise. New focus areas, particularly the development and use of patient-derived induced pluripotent stem cells for ALS disease modeling and drug screening, are being investigated as novel approaches to ALS therapeutic interventions.

In June 2007, the DoD redirected $5M to FY07 Army Research, Development, Test, and Evaluation funding for the CDMRP to initiate the Amyotrophic Lateral Sclerosis Research Program (ALSRP) as a broadly competed, peer- and programmatically reviewed research program. 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 $46M, including $7.5M in FY14.

**ALS Association*

FY07–FY13 ALSRP Research Portfolio**



***Analysis by number of awards.*

ALSRP Achievements

Chemical Genetic Screens for TDP-43 Modifiers and ALS Drug Discovery

Pierre Drapeau, Ph.D., University of Montreal

ALS is a late-onset progressive neurodegenerative disease for which no curative therapy exists. A majority of ALS cases are sporadic, although approximately 10% are linked to familial ALS incidence. Recent findings have shown that the TARDBP gene, which encodes for the DNA/RNA binding protein TDP-43, is mutated in familial ALS cases and is a major contributing factor to ALS progression. Development of novel therapies targeting TDP-43 activity may be beneficial for at least a subset of individuals with ALS. Dr. Pierre Drapeau, with support from an ALSRP FY10 Therapeutic Development Award, has sought to perform large drug screens to identify chemical modifiers of TDP-43 as therapeutic approaches to ALS treatment. He and his colleagues previously developed three in vivo genetic models of ALS by expressing a mutant TARDBP gene in worms, zebrafish, and mice. All models were shown to demonstrate an impaired mobility phenotype similar to human ALS. Under the ALSRP award, Dr. Drapeau's team performed a screen of thousands of FDA-approved drugs in their worm model and identified a number of promising compounds that restored mobility. Several of these compounds were confirmed to restore mobility in zebrafish studies (**Figure 1**). Interestingly, a majority of those compounds were neuroleptics, including the antipsychotic drug pimozide. He then conducted additional screens to find compounds that are structurally similar to these drugs, and tested pimozide derivatives on both worm and zebrafish models. Current studies to confirm these potential drug candidates in an ALS mouse model are ongoing, and the preliminary results are promising. The results from this study provide encouraging evidence for the use of TDP-43 chemical modifiers as a therapeutic for ALS. Given the positive preliminary results, and that pimozide is an FDA-approved drug, Dr. Drapeau is concurrently participating in a collaboration outside of his ALSRP award to initiate a Stage IIb randomized clinical trial to look at the effects of pimozide in patients with ALS.

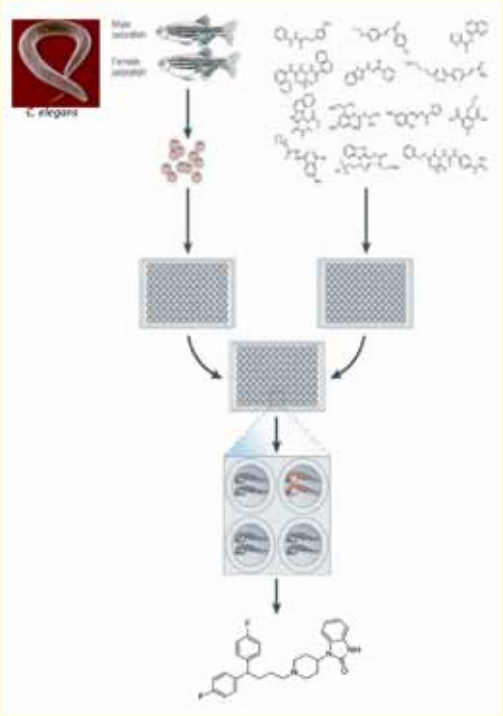


Figure 1. Chemical Genetic Screens in ALS

Neuroprotective Small Molecules for the Treatment of Amyotrophic Lateral Sclerosis: The Investigation Continues

Serge Przedborski, M.D., Ph.D., Columbia University

ALS is a progressive neurodegenerative disease for which there is no cure. The hallmark of ALS is the death of motor neurons (MNs), cells in the spinal cord responsible for movement and breathing. This disease presents itself in two different forms: sporadic or familial. The sporadic form comprises 90% to 95% of those living with ALS, yet to this day there are no known risk factors for the disease, whereas the familial form is inherited. Currently, sporadic ALS is linked to over 150 different mutations in the antioxidant enzyme superoxide dismutase-1 (SOD1) gene. All of the SOD1 mutations generally lead to muscle weakness, muscle wasting, and eventual death. Supported by an FY07 ALSRP Therapeutic Development Award, Dr. Serge Przedborski set out to speed up needed drug testing of compounds to treat ALS. Previously, it was demonstrated, by Dr. Przedborski and others, that astrocytes contain the mutated forms of SOD1 responsible for killing MNs in the spinal cord. Dr. Przedborski made use of this finding under his Therapeutic Development Award, and he successfully developed a rapid, high-throughput cell-based screen that uses astrocyte-conditioned medium and embryonic stem MNs (ES-MNs) to screen large drug libraries of already existing compounds. These screens provided a simple read-out of cell survival. Drugs that diminished the toxic effects on ES-MNs underwent further evaluation and more extensive testing. Following these tests, JNK2/3 inhibitors and Necrostatin-1 emerged as the main protective finds for both primary MNs and ES-MNs. Encouraged by these promising results, and given that much less JNK2/3 inhibitor is required for a positive result, Dr. Przedborski tested a JNK inhibitor on human spinal MNs in the presence of human astrocytes with mutant SOD1 and observed the same neuroprotective behavior as seen in rodent co-cultures. The results obtained during Dr. Przedborski's FY07 award assured him funding from other sources to continue exploring both Necrostatin-1 and various JNK inhibitors. To date, Dr. Przedborski is conducting in vivo animal studies using both drug candidates, in hopes of moving us closer to a therapeutic treatment for ALS.

Autism Research Program

VISION
Improve the lives of individuals with autism spectrum disorder now

MISSION
Promote innovative research that advances the understanding of autism spectrum disorders and leads to improved outcomes

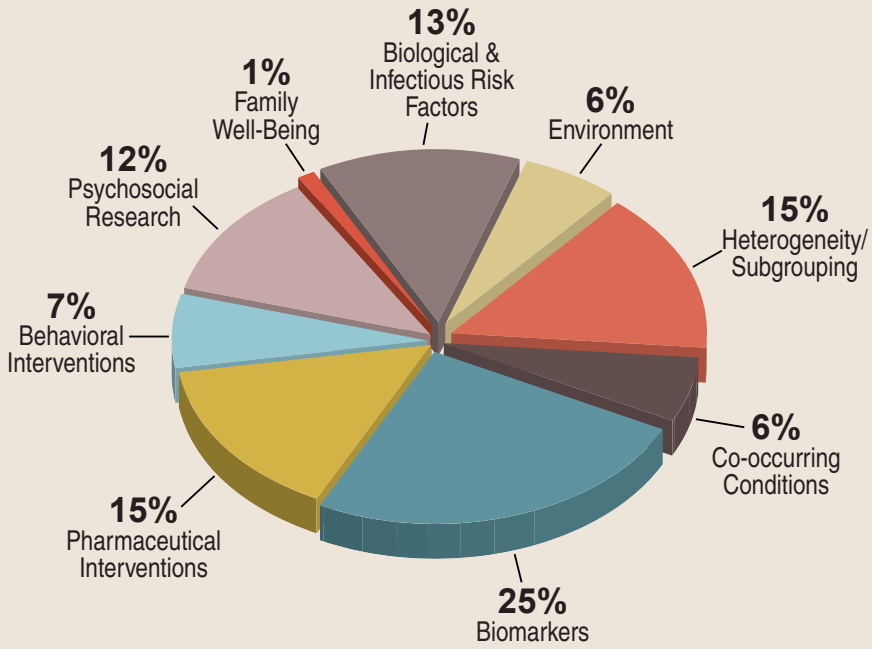
Craig Powell, M.D., Ph.D.
FY14 ARP Integration Panel Chair
"I am proud to serve as Chair of an ARP Integration Panel that always bears in mind first and foremost the needs of people with autism and their families."

Program History

With the alarming increase in the reported incidence of Autism Spectrum Disorder (ASD), Congress answered the concerned call of parents and advocates by appropriating funds for the DoD Autism Research Program (ARP) in FY07. Recent reports by the CDC indicated that the prevalence of ASD may be as high as 1 in 68. According to the report, an estimated 1 in 42 boys and 1 in 189 girls are affected and, thus, are identified as living with ASD*. Since its inception in FY07 through FY14, appropriations totaling $53.4M have been directed to the ARP to promote innovative research that advances the understanding of ASD and improves the lives of those living with ASD. The immediacy of the ARP Vision, to improve the lives of individuals with autism now, has imparted a strong sense of action and continues to steer the investment strategy for the ARP. ASD encompasses a range of complex developmental disorders characterized by mild to severe challenges in social, emotional, and communication abilities. 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.

**Morbidity and Mortality Weekly Report 63 (2014) 2–24.*

FY07–FY13 ARP Areas of Interest**



***Analysis by research funding dollars invested.*

ARP Achievements

Yun-Fai Lau, Ph.D., of the Veterans Affairs Medical Center, University of California, San Francisco, discovered a potential cause of sexual bias in autism by showing that the Y chromosome encoded transcription factor sex-determining region Y (SRY) regulates the X chromosome encoded monoamine oxidase A, an important enzyme in deamination of neurotransmitters, thus demonstrating a novel mechanism of sexual dimorphism for neural function and potential disorders.

Wu JB, Chen K, Li YM, et al. (2009) Regulation of monoamine oxidase A by the SRY gene on the Y chromosome. *FASEB J* 23:4029-38.

Andrew Feinberg, M.D., M.P.H., and Walter Kaufmann, M.D., of Johns Hopkins Medical Center and Children's Hospital, Boston, respectively, isolated differentially methylated regions within the genome of patients with autism as compared to their monozygotic twin. These epigenetic changes may help to determine if environmental factors influence the development of neurological disorders such as autism.

Ladd-Acosta C, Hansen KD, et al. (2013) Common DNA methylation alterations in multiple brain regions in autism. *Mol Psychiatry* Sep 3. 114.

Brooke Ingersoll, Ph.D., from Michigan State University developed an internet-based training program, ImPACT Online, a highly innovative, web-based, distance learning program that teaches parents to support their child's social communication development using a novel blend of evidence-based intervention techniques. ImPACT Online uses effective adult learning tools to help parents learn the intervention techniques and integrate them into their daily interactions with their child.

Ingersoll B and Wainer A. (2013) Initial efficacy of project ImPACT: A parent-mediated social communication intervention for young children with ASD. *J Autism Dev Disord* 43: 2943-52.

Armin Alaedini, Ph.D., from Columbia University used samples from a cohort of well characterized patients diagnosed with autism, their neurotypical siblings, and unrelated controls to find that patients with autism had Immunoglobulin G antibodies to gluten linked to gastrointestinal symptoms which were different than that of celiac disease. Dr. Alaedini received an FY13 Idea Development Award for *Proteomic Mapping of the Immune Response to Gluten in Children with Autism*.

Lau NM, Green PH, Taylor AK, et al. (2013) Markers of celiac disease and gluten sensitivity in children with autism. *PLoS One* 8(6):e66155.

Eric Klann, Ph.D., from New York University showed that increased EIF4E gene expression in mice results in aberrant behaviors reminiscent of autism. The results from this study resulted in a collaboration with Egenix Pharmaceuticals to conduct pre-clinical testing of compounds that will target EIF4E for the treatment of ASD.

Santini E, Huynh TN, MacAskill AF, et al. (2012) Exaggerated translation causes synaptic and behavioural aberrations associated with autism. *Nature* 493:411-415.

Trista Matascastillo, FY13 ARP Consumer Peer Reviewer

"Being part of the CDMRP process is a huge honor and an extremely important role in ensuring the advancement of care of our loved ones. Being part of the process has helped me realize that, as a consumer, I am an expert in the care of my loved ones, and I can offer unique understanding and insight that researchers and scientist value."

Barbara Buckman, FY13 ARP Consumer Peer Reviewer

"What an eye-opening experience it was to serve as a consumer reviewer for future autism research funded by the Department of Defense. As a military parent of a child with autism, I came away with such hope that autism is being taken seriously and parental input is not only respected but sought out. Please keep funding this tremendously valuable research."

Bone Marrow Failure Research Program

VISION

To understand and cure bone marrow failure disease

MISSION

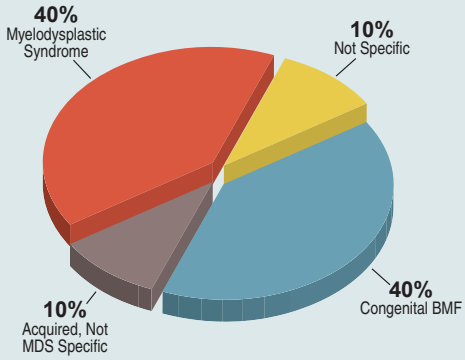
To encourage and support innovative research that is committed to advancing the understanding of inherited and acquired bone marrow failure diseases, thereby improving the health of affected individuals, with the ultimate goals of prevention and cure

Program History

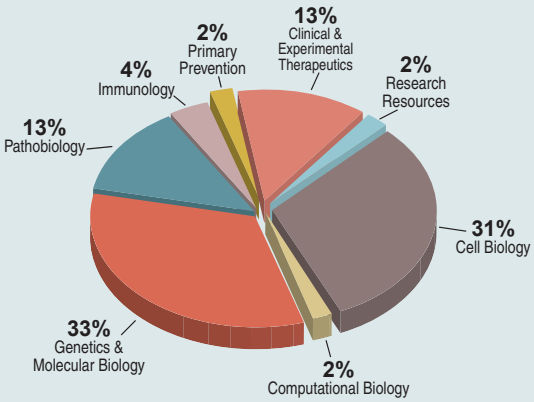
In FY08, Congress appropriated $1M for Bone Marrow Failure research. With continued appropriations, the Bone Marrow Failure Research Program (BMFRP) was established. From FY08 through FY13, $20.2M has been appropriated by Congress to research the prevention, causes, and treatment of bone marrow failure diseases. The FY14 BMFRP appropriation is $3.2M.

Bone marrow failure is a general term covering many different diseases. Bone marrow, the sponge-like tissue found inside bones, contains blood-forming stem cells which 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, in turn, 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: acquired bone marrow failure and inherited bone marrow failure. The main objective of the BMFRP is to encourage researchers to bring their best and brightest ideas to be funded in order to enhance the field and encourage innovative thinking with ingenious solutions and paradigm-shifting findings.

Classification of BMF: Percentage of Dollars Invested



BMFRP: Percentage of Dollars Invested per Research Area



Natasha McKee, FY13 BMFRP Consumer Peer Reviewer

"I thoroughly enjoyed working with the CDMRP. Everyone I interacted with was helpful and considerate plus knowledgeable and efficient. Learning more about current bone marrow failure research made me feel empowered regarding my own disease process."

BMFRP Achievements

Charles Lin, Ph.D., demonstrated the critical role of regulatory T cells in maintaining immune privilege mechanisms of the HSPC niche. This work has established a novel concept of immune-privilege in the HSPC niche and uncovered its molecular and cellular mechanisms.

Fujisaki J, Wu J, et al. (2011) In vivo imaging of Treg cells providing immune privilege to hematopoietic stem-cell niche. *Nature* 474: 216- 220.
http://cdmrp.army.mil/bmfrp/research_highlights/13lin_highlight

Jose Cancelas, M.D., Ph.D., investigated the mechanism of hematopoietic stem cell recovery after stress (ionizing radiation, chemotherapy). Deficiency in the protein connexin-43 (Cx43) highly influenced hematopoietic recovery. Results indicated that Cx43 mediates the transfer of reactive oxygen species within the bone marrow environment.

Taniguchi Ishikawa E, Gonzalez-Nieto D, et al. (2012) *PNAS* 109: 9071-9076; Gonzalez-Nieto D, Li L, et al. (2012) *Blood* 119: 5144-54.

Yi Zhang, M.D., Ph.D., discovered that both Notch and Ezh2 are critical for modulating inflammatory T-cell responses that mediate graft versus host disease and bone marrow failure.

He S, Xie F, et al. (2013) The histone methyltransferase Ezh2 is a crucial epigenetic regulator of allogeneic T-cell responses mediating graft-versus-host disease. *Blood* 122: 4119-28.
http://cdmrp.army.mil/bmfrp/research_highlights/13zhang_highlight

Omar Abdel-Wahab, M.D., showed that deletion of Asxl1, a protein co-factor important in epigenetic regulation of gene transcription, resulted in hallmark features of Myelodysplastic disorders, thus creating a disease-relevant genetically accurate model of Myelodysplastic disorders.

Abdel-Wahab O, Gao J, et al. (2013) Deletion of Asxl1 results in myelodysplasia and severe developmental defects in vivo. *J Exp Med* 210: 2641-2659.

Martin Prager, FY13 BMFRP Consumer Peer Reviewer

"When I experienced bone marrow failure and a subsequent successful stem cell transplant, I made an involuntary quantum leap into a new world, a parallel universe of physicians, procedures, and medicines unlike anything I ever experienced or imagined.
When I started my service as a consumer reviewer for BMFRP, it was another quantum leap into a parallel universe of genetic science populated with incredibly knowledgeable, altruistic people. The experience was both real, because I was actually part of it, and surreal in its unfamiliar terrain. The realization that I was participating in the kind of process that led ultimately, years ago, to the bone marrow transplant process we know today, was a fascinating experience and helped me appreciate my transplant even more."

Examples of inherited bone marrow failure diseases:

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

Examples of acquired bone marrow failure diseases :

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

Breast Cancer Research Program

VISION

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

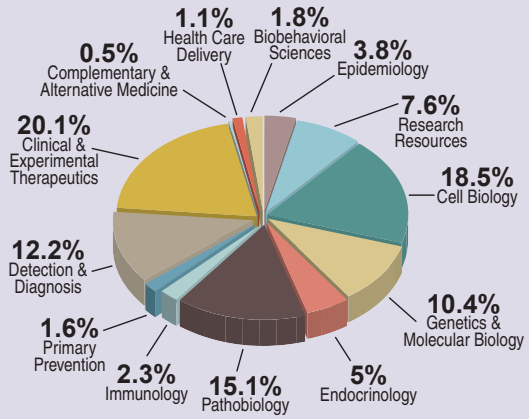
Sandi Spivey,
BCRP Consumer Reviewer

"For more than ten years, I and thousands of other breast cancer advocates, have pushed beyond the belief that raising awareness leads to eradicating the disease. What will make a difference is participating in the establishment of research priorities, providing meaningful feedback during research proposal reviews, and working side-by-side with breast cancer investigators. The BCRP is an excellent venue for the advocacy community to take a leadership role in ending breast cancer."

Program History

The Breast Cancer Research Program (BCRP) plays a leading role in the fight against breast cancer. The BCRP was established in 1992 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 $3.0B in congressional appropriations through FY14. The BCRP challenges the scientific community to design research that will address the urgency of ending breast cancer. The BCRP seeks to make breakthroughs in breast cancer, accelerate high-impact research with clinical relevance, and encourage innovation and creativity.

FY92–FY13 BCRP Research Portfolio*



**Analysis by number of awards.*

Overarching Challenges

Despite the significant progress that has been made in the breast cancer field, the BCRP recognizes that many overarching questions still remain unanswered, and that funding must be invested in critical areas of research in order to make breakthroughs that will save lives and lead to eradication of this disease. To meet this urgent need, the FY14 BCRP took two new approaches:

- The BCRP prepared a brief overview of the breast cancer landscape (http://cdmrp.army.mil/bcrp/pdfs/bc_landscape.pdf). The intent was to provide applicants with a concise overview covering the topics that are most pertinent to the BCRP's vision.
- Each FY14 BCRP application was required to address at least one of the following overarching challenges, or otherwise justify another overarching challenge related to the breast cancer landscape:
  - Prevent breast cancer (primary prevention)
  - Identify what makes the breast susceptible to cancer development
  - Determine why some, but not all, women get breast cancer
  - Distinguish aggressive breast cancer from indolent 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 life-threatening metastasis
  - Determine why/how breast cancer cells lay dormant for years and then re-emerge (recurrence); determine how to prevent recurrence
  - Revolutionize treatment regimens by replacing interventions that have life-threatening toxicities with ones that are safe and effective
  - Eliminate the mortality associated with metastatic breast cancer

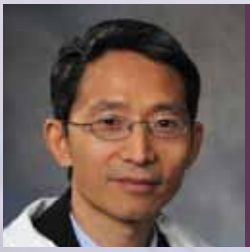
Research Breakthroughs in 2014

SARASWATI SUKUMAR, Ph.D.
JOHNS HOPKINS UNIVERSITY

Dr. Saraswati Sukumar and colleagues have created a test that can detect metastatic breast cancer with efficiency better than any test currently used. The test will also monitor a patient's response to treatment far more quickly than conventional tests, and it may allow doctors to make adjustments and avoid ineffective, unnecessary treatments. Developed with an FY03 BCRP Center of Excellence Award, the test detects breast cancer by sampling the patient's blood for DNA methylation. Not all genes are active all of the time, and one way a gene can be silenced is through the attachment of methyl molecules to the gene's promoter region – the part of a gene that controls where and to what extent a gene is activated. This otherwise normal method of gene repression can tip the balance from a gene network that functions normally to one that is cancerous. In work spearheaded by co-investigator Dr. Mary Jo Fackler, Dr. Sukumar and colleagues developed a test called "cMethDNA," a multiplexed polymerase chain reaction assay that measures the level of methylation in 10 genes known to be hypermethylated in breast cancer. In pilot studies published in *Cancer Research*, cMethDNA detected metastatic breast cancer from the blood serum of patients, with higher than 90% sensitivity and specificity. Dr. Sukumar and her multidisciplinary team are now working to validate the assay in a prospective clinical study.

VALERIE WEAVER, Ph.D.
UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

Dr. Valerie Weaver's research focuses on the biophysical characteristics of tumor cells and the tumor microenvironment. With funding from an FY04 Era of Hope Scholar Award, Dr. Weaver found that elevating mammary cell tension promotes tumorigenesis, and that cellular tension drives tumor aggression by inducing epithelial-to-mesenchymal transition. Aggressive types of breast cancers, such as triple-negative breast cancer, were found to have elevated tissue tension. In FY12, Dr. Weaver received BCRP funding to mechanistically define how tissue tension regulates tumor aggression. One aspect of tissue tension that she is studying is the glycocalyx. The glycocalyx is the exterior cell surface layer across which information flows from the cell microenvironment to signal transduction pathways originating at the plasma membrane. Dr. Weaver found that the glycan/glycoprotein (sugar) composition of the glycocalyx plays a key role in the spatial organization and function of integrins. These cell surface molecules not only modulate cell–cell and cell–matrix interactions, but also transmit signals to promote tumor cell growth and survival. Dr. Weaver's findings, published in *Nature*, show that a glycocalyx rich in sugars facilitates integrin clustering into adhesions and applies tension to matrix-bound integrins, promoting a cancer phenotype. Clinical studies conducted by Dr. Weaver revealed that large glycoproteins are abundantly expressed on circulating tumor cells from patients with advanced breast cancer. Thus, a bulky glycocalyx, or thick "sugar coating," is a novel feature identified in breast tumor cells that could promote metastasis.



YI LI, Ph.D.
BAYLOR COLLEGE OF MEDICINE

Epidemiological studies have shown that a pregnancy before age 22 lowers a woman's risk of breast cancer, while pregnancies that begin after age 35 increase breast cancer risk. It is unclear what pregnancy-associated changes can increase cancer risk. Supported by BCRP funding, Dr. Yi Li identified a key protein that, during pregnancy, allows precancerous cells to evade the body's natural defenses that normally keep cell proliferation in check. With BCRP funding early in his career, Dr. Li developed a novel mouse model that closely mimics breast cancer initiation in humans. Using this model, he tested the hypothesis that first pregnancies impart different effects on breast cancer risk due to divergent amounts of mutations in the breast cells in younger versus older women. Dr. Li found that the transcription factor, STAT5, contributed to tumorigenesis in pregnant mice through the suppression of apoptosis in early breast lesion cells, thereby increasing their tendency to become cancerous. Dr. Li's most recent findings, published in *eLIFE*, have shown that active STAT5 is detectable in human breast lesions, especially in women who have had a pregnancy. Interestingly, the remodeling of breast tissue during pregnancy – specifically, changes in expression levels of lactation hormones – stimulates STAT5 and consequently weakens the cellular mechanisms that kill off precancerous cells by apoptosis. Based on these findings, STAT5 could represent a potential target to prevent and/or reduce the risk of breast cancer in pregnant women over the age of 35. Dr. Li is partnering with industry to conduct a clinical trial to test a STAT5 inhibitor in pre- and post-menopausal women.

"I am extremely grateful to the DoD BCRP for its generous support of my research program at Baylor as well as my postdoctoral research training. This support has allowed me to explore some very risky research ideas. I am gratified that some of these ideas have generated potential clinical significance, and we are excited to now be moving toward a clinical trial." —Yi Li, Ph.D.

Breast Cancer Research Semipostal Program

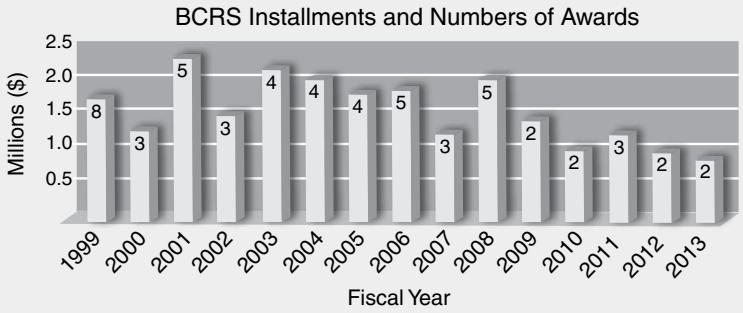
Program History

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. Net revenues from sales of the BCRS, which costs 55 cents, are provided to two designated funding agencies, the DoD BCRP and the NIH, to support breast cancer research. Public Law 110-80 reauthorized the BCRS through December 31, 2015.

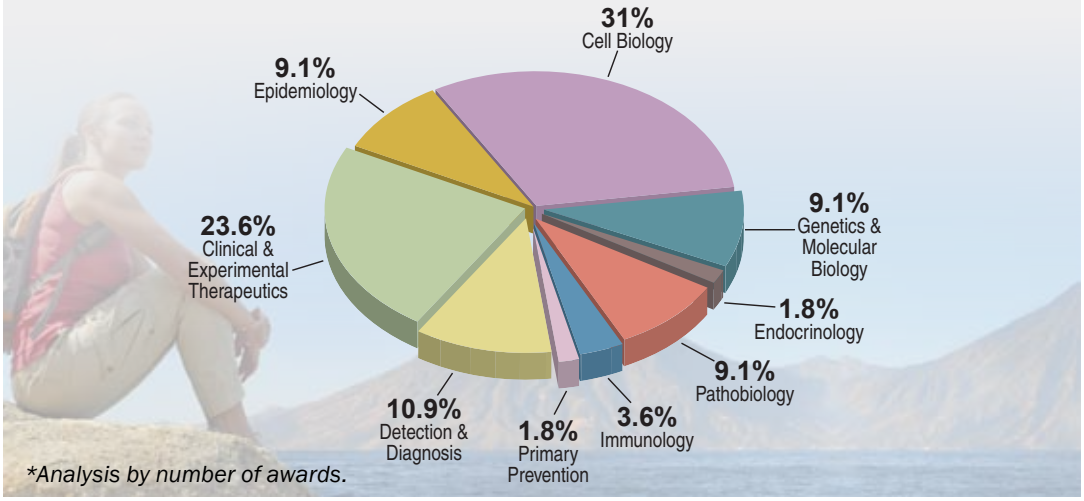
Research Awards

Breast cancer stamp funding received by the BCRP between FY99 and FY13 has been used to fully or partially fund 55 awards under three award mechanisms: 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.

Total Proceeds from BCRS	$23,106,942.91
Research	$22,005,936.31
Management Costs	$1,101,006.60



FY99–FY13 BCRS Research Portfolio*



*Analysis by number of awards.

RECENT AWARDS

FY12

- Jing Yang, Ph.D., University of California, San Diego – "Regulation of Breast Cancer Stem Cell by Tissue Rigidity"
- Filippo Giancotti, M.D., Ph.D., Memorial Sloan Kettering Cancer Center – "Autophagy and TGF-Beta Antagonist Signaling in Breast Cancer Dormancy at Premetastatic Sites"

FY13

- Seth Rubin, Ph.D., University of California, Santa Cruz – "Inhibition of Retinoblastoma Protein Inactivation"
- Geoffrey Luke, Ph.D., University of Texas at Austin – "Noninvasive Label-Free Detection of Micrometastases in the Lymphatics with Ultrasound-Guided Photoacoustic Imaging"

Research Highlights

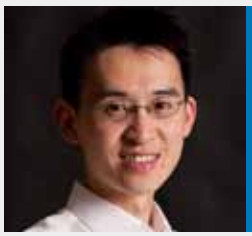
Modulation of Regulatory T Cells as a Novel Adjuvant for Breast Cancer Immunotherapy

GAYATHRI DEVI, Ph.D., DUKE UNIVERSITY

Immune therapies have shown some success for the treatment of breast cancer, but the efficacy of these therapies has been limited by the activity of immunosuppressive T cells (Treg). Treg cells suppress antitumor immunity by decreasing the immune response to tumor-associated self-antigens such as HER2, which is widely used as a target for breast cancer immunotherapy. Dr. Gayathri Devi of Duke University had previously shown that Treg levels are higher in cancer patients as compared with healthy volunteers and that they are especially high in patients with advanced breast cancer, suggesting that suppressed immunity caused by high Treg levels contributes to breast cancer progression.

Two proteins are known to be associated with maintaining the immunosuppressive function of Treg cells: transforming growth factor beta 1 (TGFbeta-1) and forkhead box protein 3 (FOXP3). With support from an FY06 BCRP Idea Award, Dr. Devi built upon her previous work and hypothesized that inhibition of Treg activity by blocking TGFbeta-1 or FOXP3 function would enhance the antitumor effect of immunotherapies, such as those that target the receptor HER2. Dr. Devi and her team developed several novel ways to inhibit TGFbeta-1 and FOXP3, and generated novel anti-HER2 vaccines. They also established that FOXP3 expression is not restricted to T-cell lineage and demonstrated for the first time that FOXP3 is expressed in the most aggressive subset of breast cancer cells – called inflammatory breast cancer cells. Analysis of recurrence-free survival data from a collection of 23 datasets posted on the National Center for Biotechnology Information Gene Expression Omnibus database revealed high expression of FOXP3 significantly associated with higher risk of recurrence in triple-negative breast cancer. Proof-of-principle experiments showed that inhibition of TGFbeta-1, in combination with anti-HER2 therapy, led to a dramatic decrease in tumor growth in mice as compared with tumor growth following either treatment alone. Inhibition of FOXP3 expression caused depletion of the immunosuppressive, FOXP3+ Treg cells and enhanced antigen-specific T-cell reactivity of human peripheral blood mononucleocytes. This work provides strong evidence for use of TGFbeta-1 and FOXP3 inhibitors in combination with immune-based therapies for the treatment of breast cancer.

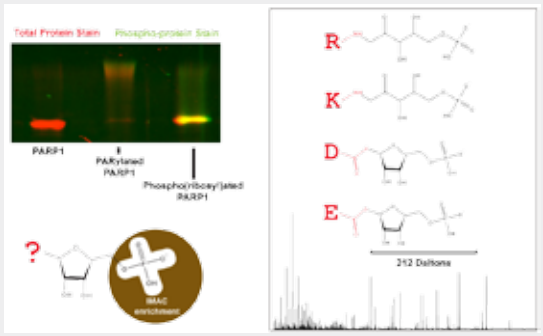
The Role of Poly(ADP-Ribose) in MicroRNA Activity in Breast Cancers



ANTHONY LEUNG, Ph.D., JOHNS HOPKINS UNIVERSITY

Inhibitors of poly(ADP-ribose) polymerase 1 (PARP-1) have shown promise in clinical trials for breast cancer patients. PARP-1 is the first identified polymerase of a protein superfamily, which consists of 17 PARP family members. PARP proteins are crucial components of a cell's DNA repair machinery, and recent studies suggest that they may also decrease the activity of microRNAs, which are master regulators of gene expression. Because current inhibitors target the PARP-1 catalytic domain, which is similar to the catalytic domain of all PARP protein family members, it is not clear which PARP proteins account for the therapeutic effects seen with these inhibitors. Dr. Anthony Leung, recipient of an FY10 Idea Award, sought to elucidate how PARP family members regulate microRNA and how this contributes to breast cancer progression. A clearer understanding of PARP function and microRNA regulation could lead to the development of more specific PARP inhibitors.

However, one major problem in furthering the mechanistic studies of PARP's role in microRNA regulation is the lack of proteomics techniques that can identify PARP-modified sites. PARP is a class of protein modification enzymes that adds polymers of ADP-ribose units onto proteins in cells. Due to the heterogeneous length of these polymers, it is difficult to use mass spectrometry (the most common and powerful proteomics tool available) to identify sites on proteins that have been modified by PARP. Through the support of the Idea Award, Dr. Leung and his team have devised an enzymatic strategy to tackle the heterogeneity problem, and they recently succeeded in developing a mass spectrometry method to identify PARP-modified sites from cells (Daniels et al., *Journal of Proteome Research* 2014). The ability to identify these sites on microRNA regulatory proteins will allow mechanistic studies on how PARP regulates microRNA activities in breast cancers.



As several PARP inhibitors are currently in Phase III clinical trials for breast cancer, it is important to identify which PARP-modified proteins are inhibited by these drugs. Therefore, the successful clinical application of this method on patient samples will likely offer new insights into the therapeutic benefits and side effects of this promising class of drugs for breast cancer patients.

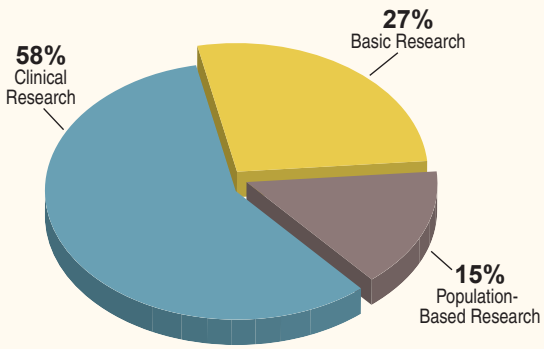
Defense Medical Research and Development Program

MISSION

To provide full life-cycle operational management support to the Defense Medical Research and Development Program, a core Department of Defense research program within the Office of the Assistant Secretary of Defense for Health Affairs

Program History

FY10–FY13 DMRDP Research Portfolio*



**Analysis by number of awards.*

The CDMRP provides operational execution management support for the Office of the Assistant Secretary of Defense for Health Affairs (OASD[HA]) Defense Medical Research and Development Program (DMRDP). The DMRDP was established in FY10 under the Defense Health Program, with a focus on advancing the state of medical science in those areas of most pressing need and relevance to today's battlefield experience. The objectives of the DMRDP are to discover and explore innovative approaches to protect, support, and advance the health and welfare of military personnel, families, and communities; to accelerate the transition of medical technologies into deployed products; and to accelerate the translation of advances in knowledge into new standards of care for injury prevention, treatment of casualties, rehabilitation, and training systems that can be applied in theater or in the clinical facilities of the Military Health System.

The OASD(HA) assigned execution management responsibilities to the USAMRMC as one of several execution agents to provide strategic and operational management support for the DMRDP. The research program areas of responsibility assigned to USAMRMC include:

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

Each of these major research program areas is managed by a committee, called a Joint Program Committee, or JPC, which consists of DoD and non-DoD medical and military technical experts. Within the USAMRMC, operational and research award management support is provided primarily by CDMRP in coordination with advanced development agencies as appropriate.

CDMRP Portfolio Execution Assignments

From FY10–FY13, the CDMRP has managed 142 awards totaling approximately $244M in support of the DMRDP, funding basic, translational, and clinical research efforts. These projects are expected to yield critical prevention, detection, diagnosis, treatment, and rehabilitation and reintegration strategies for the nation's Service Members, veterans, and their family members.

The primary research areas targeted by the DMRDP include TBI, psychological health (including post-traumatic stress disorder), polytrauma and blast injury, wound infection, blood products and safety, operational health and performance, rehabilitative medicine, and device development.

Research to Advance and Accelerate

Awards supported by the DMRDP 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. Although the primary mission of DMRDP research focuses on military relevance, the benefits often extend to the general public as well. The following are recent examples by key program research areas.

Military Infectious Diseases Research Program (MIDRP, JPC-2)

- **Lipid Peroxidation as a Biomarker of High Susceptibility to Blast Wound Infection**, Laurence Rahme, Ph.D., Massachusetts General Hospital
- **A First-in-Human Phase I Clinical Study of ACHN-975, a First-in-Class Agent Being Developed for the Treatment of Serious Multidrug-Resistant Gram-Negative Bacterial Infections**, Kenneth Hillan, M.B., Ch.B., Achaogen, Inc.
- **Persistence of Antibiotic Resistance Plasmids in Biofilms**, Eva Top, Ph.D., University of Idaho
- **The Potential Application and Risks Associated With the Use of Predatory Bacteria as a Biocontrol Agent Against Wound Infections**, Daniel Kadouri, Ph.D., University of Medicine and Dentistry of New Jersey

Combat Casualty Care Research Program (CCCRP, JPC-6)

- **Biomarker Signatures in Blood for Acute and Chronic mTBI Using the SOFIA Technology**, Richard Rubenstein, Ph.D., State University of New York, Downstate Medical Center
- **Development of Predictive Models of Injury for the Lower Extremity, Lumbar, and Thoracic Spine after Discharge from Physical Rehabilitation**, Daniel Rhon, D.Sc., DPT, Madigan Army Medical Center
- **Pre-clinical and Clinical Development of Low-Dose Methamphetamine for the Treatment of Traumatic Brain Injury**, David Poulsen, Ph.D., University of Montana
- **Low-level Laser Therapy for Traumatic Brain Injury**, Benjamin Vakoc, Ph.D., Massachusetts General Hospital

Military Operational Medicine Research Program (MOMRP, JPC-5)

- **Biomechanical Modeling and Measurement of Blast Injury and Hearing Protection Mechanisms**, Rong Gan, Ph.D., University of Oklahoma, Norman
- **Neuromodulation as a New Treatment for Post-Traumatic Stress Disorder in Veterans: Evaluating the Effectiveness of Trigeminal Nerve Stimulation**, Andrew Leuchter, M.D., University of California, Los Angeles
- **Peer-Led Suicide Prevention: Promoting Healthy Family Role Transitions for Military Personnel**, Peter Wyman, Ph.D., University of Rochester
- **HomeFront Strong: Building Resiliency in Military Families**, Michelle Kees, D.O., University of Michigan

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

- **Safety and Efficacy of the BrainPort V100 Device in Individuals Blinded by Traumatic Injury**, Patricia Grant, Ph.D., Wicab, Inc.
- **EphB1 as a Novel Drug Target to Combat Pain and Addiction**, Mark Henkemeyer, Ph.D., University of Texas Southwestern Medical Center at Dallas
- **Biomimetic Delivery of Biomolecules for Craniofacial Bone Regeneration**, Peter Ma, Ph.D., University of Michigan
- **Hearing Preservation Electrodes in Veterans and Military Servicemembers With Noise-Induced Hearing Loss**, Marlan Hansen, M.D., Iowa City VA Medical Research Foundation

Duchenne Muscular Dystrophy Research Program

VISION

To extend and improve the function, quality of life, and life span for all individuals diagnosed with DMD

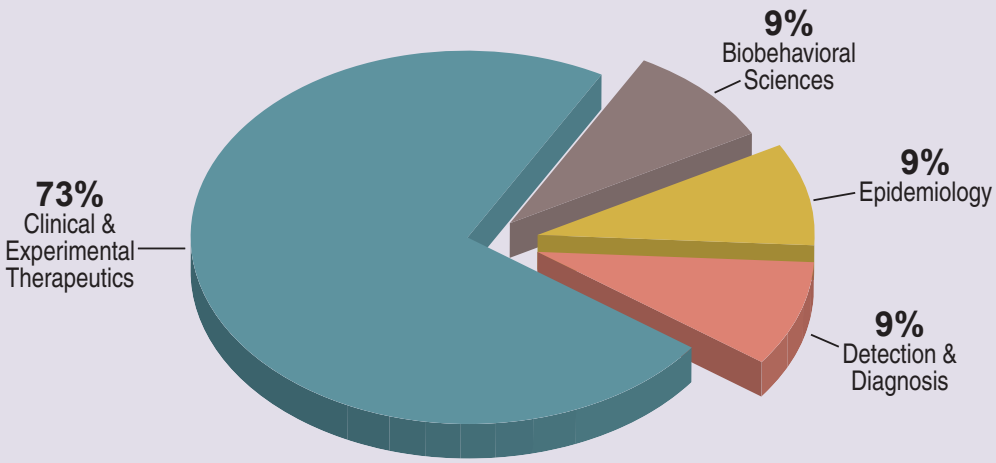
MISSION

To better inform the development of drugs, devices, and other interventions and promote their effective clinical testing

Program History

The Duchenne Muscular Dystrophy Research Program (DMDRP) was established in FY11 as a result of the passionate and tireless efforts of Duchenne Muscular Dystrophy (DMD) advocates. The initial congressional appropriation for DMDRP was $4M, followed by appropriations of $3.2M for FY12 through FY14, for a total of $13.6M. Over the past several years, research has identified many new potential therapeutic targets, and has significantly expanded the number of potential therapeutics in the pipeline for DMD. In order to assist in the development of treatments for DMD, the DMDRP has focused on accelerating promising therapeutic ideas into clinical applications and supporting the training of new physician researchers to facilitate their pursuit of careers in DMD research. DMD affects approximately 1 out of every 3,500 male infants (about 20,000 new cases a year). This form of muscular dystrophy results from mutations in the dystrophin gene, which leads to an absence of dystrophin in muscle cells, allowing these cells to be easily damaged. Boys living with DMD experience devastating muscle weakness that affects the skeletal muscles, heart, and respiratory muscles. Symptoms of DMD typically develop prior to age 5, and by age 12 most patients are confined to a wheelchair. Young men with DMD rarely live beyond their early 30s. A much milder version of DMD is Becker muscular dystrophy. The onset of Becker muscular dystrophy usually occurs in the teens or in early adulthood, and the course of the disease is slower and less predictable than for DMD.

FY11–FY13 DMDRP Research Portfolio*



*Analysis by number of awards.

Supporting the Research Objectives of the Muscular Dystrophy Action Plan

The MD-CARE Act (Public Law 107-94) established the Muscular Dystrophy Coordinating Committee (MDCC) to coordinate research activities across the NIH and with other Federal programs and activities. In support of the MD-CARE Act, the MDCC developed an "Action Plan for the Muscular Dystrophies" to identify feasible, high-priority research objectives that could be used by the MDCC and the muscular dystrophy scientific community to coordinate research activities in order to achieve the goal of timely detection, diagnosis, treatment, and prevention of all of the muscular dystrophies. In support of this Action Plan, the DMDRP has funded projects in all the major topic areas, with the overall goal of moving promising ideas in DMD into clinical applications.

MECHANISMS

- Gail Thomas, Ph.D., is evaluating a COX-inhibiting nitric oxide donor (Naproxcinod) as a way to increase nitric oxide **to counteract functional muscle ischemia and thus improve muscle blood flow regulation and heart function** in Duchenne/Becker Muscular Dystrophy.

LIVING WITH MD

- Avital Cnaan, Ph.D., is establishing **minimal clinically important differences for current clinical trial endpoints and composite outcome measures that are sensitive and responsive to changes produced by treatments** in children and adults with muscular dystrophies.
- Craig McDonald, M.D., will be developing **a lifespan-based novel composite person-reported outcome measurement tool** using data from the CINRG Duchenne Natural History Study to evaluate treatment effects in DMD.

DIAGNOSIS AND SCREENING

- Glenn Walter, Ph.D., is evaluating near infrared imaging as a way to **monitor muscle cell response and therapeutic agent delivery** in dystrophic and damaged muscle.

THERAPY

- Paul Martin, Ph.D., is testing two different gene therapy vectors for **GALGT2 gene therapy for prevention of cardiomyopathy** in DMD patients.
- Carmen Bertoni, Ph.D., is **conducting optimization, efficacy, tolerability, and safety testing of read-through drug 13 derivatives** for DMD.
- Elizabeth McNally, M.D., Ph.D., is evaluating the use of an **LTBP4 antibody to prevent release of TGF-β** sequestered by LTBP4, and whether this will lead to **muscle stabilization and reduced fibrosis in DMD**.
- Jill Rafael-Fortney, Ph.D., is optimizing **Renin-Angiotensin-Aldosterone inhibitors as a treatment for DMD**.
- Barry Byrne, M.D., Ph.D., is developing advanced gene therapy using a **mini dystrophin gene for treatment of cardiomyopathy and respiratory insufficiency** in DMD.
- Dongsheng Duan, Ph.D., will be conducting **preclinical studies using the second-generation adeno-associated virus micro-Dystrophin vector** to support an Investigational New Drug application and future clinical trial.
- Elisabeth Barton, Ph.D., will be **developing orally bioavailable therapeutics** by the chloroplast expression system **to counter muscle degeneration, weakness, and fibrosis** in DMD.

Mindy Cameron, DMDRP Consumer Reviewer

"The DoD's commitment to this program and the stringent review process were extremely gratifying and imparted to me the knowledge that many people are working very hard to help give those diagnosed with Duchenne a chance at longer and healthier lives. A Duchenne diagnosis comes with a lot of fear and uncertainty, and for me, participating in clinical trials, advocacy, and programs like the DMDRP are constructive ways to fight against the disease that threatens my son's life."

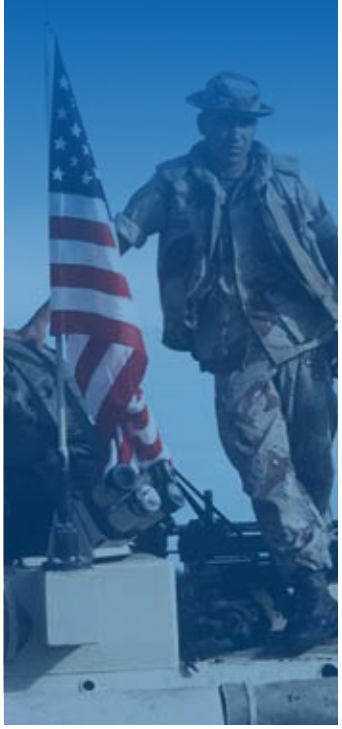
Gulf War Illness Research Program

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



Program History

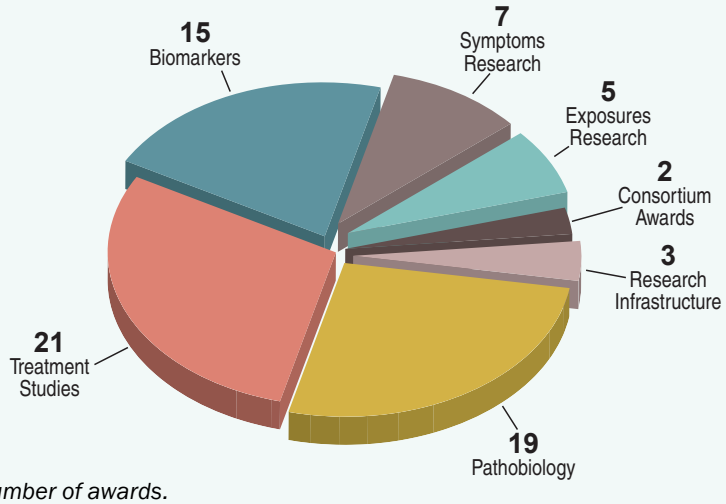
Gulf War Illness (GWI) is characterized by persistent symptoms such as chronic headache, widespread pain, cognitive difficulties, unexplained fatigue, gastrointestinal problems, respiratory symptoms, and other abnormalities that are not explained by traditional medical or psychiatric diagnoses. This complex set of chronic symptoms may affect as many as 250,000 veterans of the 1990–1991 Gulf War, of the nearly 700,000 deployed to that region. The Gulf War Illness Research Program (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.

DoD-funded GWI research began in 1994 and was funded up to FY06 through a number of organizations. In FY07, no finding was allocated to the DoD for GWI research; in FY08, the CDMRP GWIRP was inaugurated with a $10M allocation. From FY08 to FY14, the GWIRP has received a total of $84M in congressional appropriations. The program supports peer-reviewed research focused on characterizing the complex symptoms that comprise GWI, identifying objective markers (biomarkers) for the disease, understanding its pathobiology, and identifying effective treatments.

Donald Overton, GWIRP Consumer Reviewer

"As consumer reviewers for CDMRP's Gulf War Illness Research Program, we're afforded the unique opportunity of taking our experiences and incorporating them into the scientific peer review process. We get to assist the scientists in actualizing the human component of the research being proposed. This gives us a meaningful voice in the research process, and that gives us hope for the future."

FY06–FY13 GWIRP Research Portfolio*



*Analysis by number of awards.

BEATRICE GOLOMB, M.D., Ph.D., UNIVERSITY OF CALIFORNIA, SAN DIEGO

Mitochondrial Dysfunction Demonstrated in GWI

Many published studies have investigated possible links between GWI and in-theatre exposure to a number of factors such as vaccines, insect repellents, chemicals, paints, fumes, depleted uranium, and microbes. Several current studies are now investigating exposure to cholinesterase inhibitors including organophosphate nerve gas residues, pyridostigmine bromide nerve agent pretreatment pills, and carbamate and organophosphate pesticides. These cholinesterase inhibitors work by preventing the breakdown of acetylcholine at nerve synapses, but they are also known to produce toxicity via oxidative stress and mitochondrial dysfunction.

Dr. Beatrice Golomb and her team at the University of California, San Diego, set out to objectively test for mitochondrial dysfunction by using phosphorus-31 magnetic resonance spectroscopy to examine the time it takes for muscle phosphocreatine (PCr) to recover to resting levels after exercise in Gulf War veterans with GWI, comparing these to matched non-deployed controls. The rate of PCr recovery is widely considered to be a robust and practical index of mitochondrial status because PCr is a backup energy source that is depleted with exercise, and PCr recovery depends on mitochondrial adenosine triphosphate production. The study found that PCr recovery was significantly prolonged in GWI patients, as compared with controls, indicating mitochondrial dysfunction in those subjects. Results from this study show that mitochondrial pathology is present in GWI and can be noninvasively measured. Dr. Golomb plans on repeating this study in a larger number of subjects using additional tests for measuring mitochondrial function.

GORDON BRODERICK, Ph.D., NOVA SOUTHEASTERN UNIVERSITY

NANCY KLIMAS, M.D., NOVA SOUTHEASTERN UNIVERSITY

Simulations Demonstrate GWI Hormone-immune Imbalances

GWI is associated with abnormalities in the immune system, the hypothalamic-pituitary-adrenal (HPA) hormone system that controls the body's "fight or flight" response, and the system controlling sex hormones (the hypothalamic-pituitary-gonadal axis [HPG] system). Drs. Gordon Broderick and Nancy Klimas sought to use principles from engineering to better understand these abnormalities.

In control system theory, controller settings are sometimes called "operating rules," and it is understood that some combinations of settings or "rule sets" will result in smooth, stable operation while other combinations can lead to wild oscillation and run-away conditions. Normal levels of hormones, cytokines, and other factors that control the immune, HPA, and HPG systems can be thought of as a stable rule set that is maintained over a lifetime.

Because of its chronic (stable) nature, Drs. Broderick and Klimas suspected that GWI might represent a different stable rule set for these systems—stable, yet well away from the normal range of settings and behaviors. As a test, Dr. Broderick and associate Dr. Travis Craddock constructed a computer simulation of the many interactions between hormones and proteins of the immune system (**Figure 1**) as well as both male and female versions of the HPG system. They then used these simulations to identify stable rule sets for the combined systems.

Once the rule sets had been established, Dr. Klimas and colleague Dr. Mary Ann Fletcher analyzed blood from patients with GWI and Chronic Fatigue Syndrome for levels of key hormones, and they compared the experimentally measured levels with those associated with the stable rule sets. Remarkably, sex-appropriate matches were found between human subjects and the computer-predicted stable rules sets. Broderick and Craddock are now conducting further simulations to determine if it would be possible to shift the pathological stable rules sets back to normal conditions by varying levels of selected hormones and cytokines.

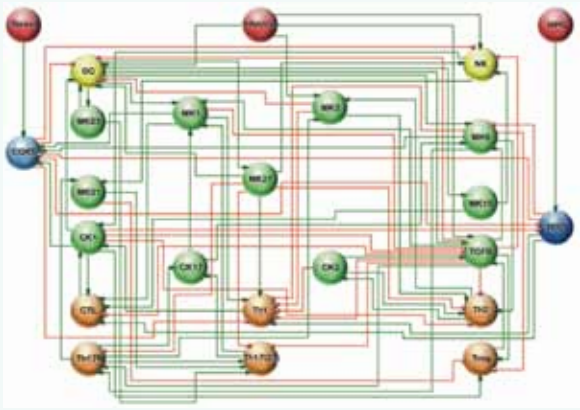


Figure 1. Wiring diagram for the immune network with hormonal inputs. *Interactions between innate cells (yellow), adaptive cells (orange), their cytokines (green), CORT (light blue), and TEST (dark blue) as activated by infection, stress, or the HPG axis (red). Green interactions indicate an activating influence, and red interactions indicate an inhibiting influence.*

Joint Warfighter Medical Research Program

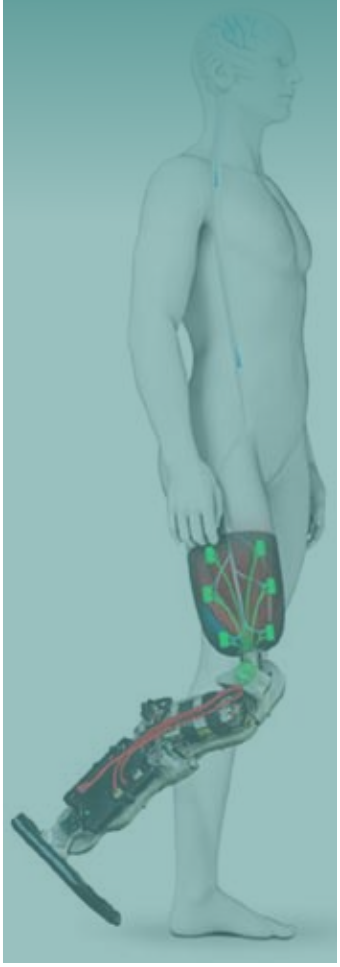
Program History

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

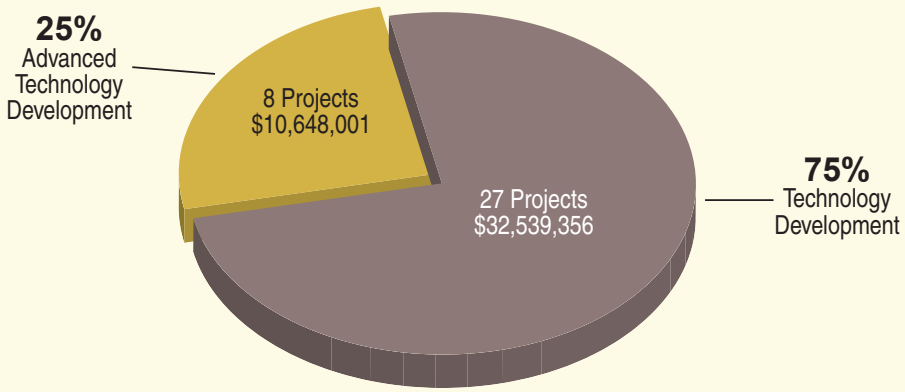
Each year, a broad spectrum of research projects are considered for funding under the JWMRP. The projects align to the six JPC scientific domains represented in the DMRDP: Medical Training and Health Information Sciences (JPC-1), Military Infectious Diseases (JPC-2), Military Operational Medicine (JPC-5), 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; it doubled the appropriation to $100M in FY14. Because the overall goal of the program is to deliver a product for the DoD, the ratio of funding allocation over the past three 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, and 35 projects are aligned to the FY13 JWMRP. The graphs below depict the demographics of the program for FY13.

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. By focusing on both early and advanced technology development, the JWMRP offers a pathway to transition products to military healthcare providers and the Warfighter.



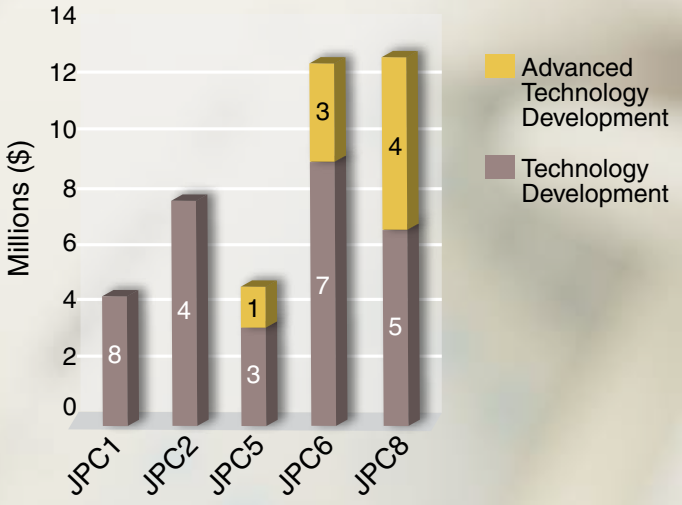
FY13 JWMRP Summary



Research Efforts Funded by the JWMRP Include:

- Prototype development and testing of a miniaturized, remotely controlled, image-guided surgical robot.
- Smart phone biofeedback game based on heart rate variability analysis to increase stress endurance.
- Intelligent tutoring system for emergency preparedness training.
- Development of a Norovirus vaccine.
- A virtual reality-based exposure therapy tool for patients who experienced military sexual trauma.
- Biomarker development and assessment for monitoring wound healing.
- A transportable pathogen reduction and blood safety system.
- A non-electric disposable intravenous infusion pump.
- Restoration therapies for SCI.
- Blood/imaging biomarkers to identify mild traumatic brain injury.
- Advancement of non-opioid analgesics for pain management.
- Modifying and enhancing lower extremity prosthetics for rehabilitation and restoration of balance and locomotion.
- A lower extremity prosthesis that adaptively recalibrates extremity neural control systems.
- Development of a ruggedized upper extremity prosthetic device.

FY13 JWMRP Funding Distribution



Transportable pathogen reduction and blood safety system

Non-electric disposable intravenous infusion pump

Lower extremity prosthesis

Ruggedized upper extremity prosthesis

Lung Cancer Research Program

VISION

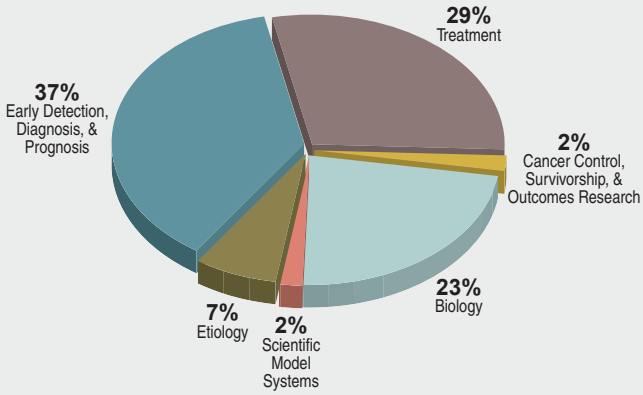
Eradicate deaths from lung cancer to better the health and welfare of the military and the American public

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

Program History

Lung cancer is the leading cause of cancer deaths in the United States. It is estimated that there will be more than 224,000 new cases of lung cancer this year, and over 159,000 associated deaths. The Lung Cancer Research Program (LCRP) was established in FY09 with a congressional appropriation of $20M. Since then, the dedicated efforts by lung cancer advocates to increase public awareness of this disease, and federal funding for its research have led to a total appropriation of $79M to the LCRP, including $10.5M for FY14. To address the critical needs of the lung cancer research and patient communities, the LCRP adapts its investment strategy annually to support underfunded and underrepresented areas. Areas of specific focus include development of non- or minimally invasive detection and screening tools, understanding the mechanisms leading to various sub-types of lung cancer and the progression to clinically significant lung cancer, prevention and treatment, predictive and prognostic markers to identify responders and non-responders, and understanding susceptibility or resistance to treatment.



FY09–FY13 LCRP Research Portfolio*

**Analysis by number of awards.*

Innovative Projects in the Pipeline

Mechanism for Clastogenic Activity of Naphthalene
Bruce Buchholz, Ph.D.
Lawrence Livermore National Laboratory

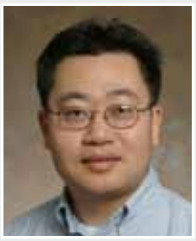
Genetic and Epigenetic Determinants of Lung Cancer Subtype: Adenocarcinoma to Small Cell Conversion
Charles Rudin, M.D., Ph.D.
Memorial Sloan Kettering Cancer Center

Exploiting Tumor-Activated Testes Proteins to Enhance Efficacy of First-Line Chemotherapeutics in NSCLC
Angelique Whitehurst, Ph.D.
University of Texas Southwestern Medical Center

Clinical Validation of a miRNA Blood Test to Identify High-Risk Individuals Eligible for Low-Dose Computed Tomography Screening for Lung Cancer Early Detection
Pier Paolo Di Fiore, M.D., Ph.D.
European Institute of Oncology

Noninvasive Personalization of Lung Cancer Therapy Using a New, Clinical-Grade Assay for Plasma-Based Measurement and Monitoring Tumor Genotype
Geoffrey Oxnard, M.D.
Dana-Farber Cancer Institute

Recent Accomplishments Making an Impact



Jing Chen, Ph.D. – Novel Therapeutic Strategy: Demonstrated that tyrosine 26 phosphorylation of the glycolytic enzyme phosphoglycerate mutase 1 (PGAM1), a common occurrence in cancer cells, provides a metabolic advantage to cancer cell proliferation and tumor growth. Translational studies using a recently developed novel PGAM1 inhibitor (PGMI-004A) exhibit promising efficacy and minimal toxicity.

Pier Scaglioni, M.D. – Targeting Oncogenic K-RAS Signaling for Therapeutic Intervention: Demonstrated that pharmacologic inhibition of focal adhesion kinase (FAK) in mutant K-RAS lung cancers with mutations in INK4a/ARF or p53 significantly reduces the viability and survival of these cancer cells. These findings led to a multicenter Phase II clinical trial of defactinib, a potent inhibitor of FAK, to treat K-RAS-mutated non-small-cell lung carcinoma (NSCLC) patients.

Maximillian Diehn, M.D., Ph.D. – Residual Disease Monitoring: Developed a non-invasive method, dubbed Cancer Personalized Profiling by Deep Sequencing (CAPP-Seq), for isolating circulating DNA from blood to detect rare, cancer-associated mutations to measure disease burden. Researchers are now working toward clinical trials to see whether CAPP-Seq can improve patient outcomes and decrease costs. This technology may be applicable across all cancers.

Mathew Meyerson, M.D., Ph.D. – Functional Genetic Mutation Analysis: Identified a somatic mutation, ARAF S214C, as a new oncogenic driver in lung adenocarcinoma and an indicator of sorafenib response. In lung squamous cell carcinoma, identified Fibroblast growth factor receptor 2 (FGFR2) and FGFR3 mutations that can be inhibited by FGFR inhibitors, providing a rationale for future clinical studies with FGFR inhibitors in patients with squamous cell lung cancer.

Deric Wheeler, Ph.D. – Prognostic Indicator and Therapeutic Target: Demonstrated that nuclear EGFR protein expression predicts poor survival in early stage NSCLC, and that nuclear EGFR may be a potential therapeutic target for re-sensitizing to cetuximab treatment in NSCLC.

Hannah Rabinowich, Ph.D. – Overcoming Drug Resistance: Established a novel mechanism of cross-regulation between autophagy and apoptosis via the Atg7/caspase-9 complex. This complex will be targeted to inhibit autophagy and enhance apoptosis to overcome tumor cell resistance to EGFR tyrosine kinase inhibitors.

Evalyn Linnea Duff, LCRP Consumer Reviewer

"I have served as a Peer Reviewer for three online cycles and one onsite review [for the LCRP]. It is intellectually challenging and a big commitment. But that is part of what I like so much about serving as a Peer Reviewer: it's hard work but you come away from it feeling as if you have made a significant contribution; it is incredibly rewarding."

Zahid H. Siddik, Ph.D., LCRP Peer Reviewer

"I have participated on a number of occasions in the CDMRP peer review process, and I have always enjoyed the participation of consumer reviewers/ advocates, who provide a constant reminder, inspiration, and a sense of urgency for why we in the scientific community must continue to play an active role in the war against cancer. Being part of the LCRP grant review process that funds innovative proposals to advance the knowledge base and lay the foundation for potential cures is one effective and satisfying way to participate in the war against lung cancer."

Military Burn Research Program

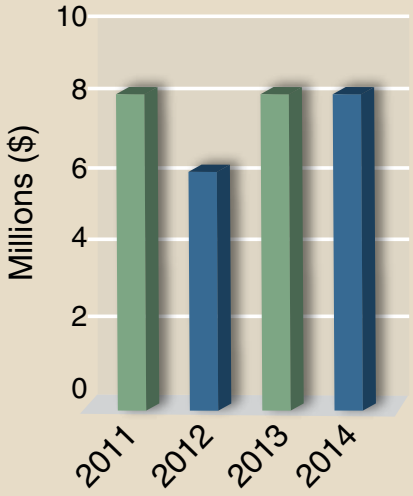
VISION

To deliver the best combat burn trauma care to improve Warfighter's health and performance outcomes

Program History

Combat burn injuries are devastating and are typically far more severe than burns in the civilian setting. Due to the polytrauma nature of the injuries received in theater, soldiers are being treated for multiple wounds resulting from a single incident such as a detonated incendiary device. Hence, in addition to burns, the soldiers may also have fractures, amputations, smoke inhalation, and head injuries at the same time. This traumatic assault adds significantly to the innate immune response, which often leads to organ damage, in addition to the injuries that are visible. Recognizing that capability gaps for treating combat burn injuries exist, the CCCRP Treatments for Tissue Injury Portfolio (TTIP) created and established a specific research program, the Army's Military Burn Research Program (MBRP) in FY11. The TTIP Portfolio Manager has the lead on this program and is responsible for setting the vision, including developing the research goals and focus areas. In FY11, the TTIP Portfolio Manager organized a steering committee of burn specialists across the services to identify the topics of interest and priority to the military burn community.

The overarching objective of the program is to address the trauma of burn, and is specific to the issues affecting the military population being injured in combat. Funding for the program comes directly from a congressional appropriation line in support of the Army's Research, Development, Testing, and Evaluation (RDTE) programs. Research topics released in each year of the solicitation are those identified as the highest prioritized capability gaps.



FY11–FY14 MBRP Appropriations

Army RDTE appropriations from FY11 to FY14 totaled $30M. To date, 18 projects have been selected and approved for funding. Performers include research hospitals and burn centers, universities, and businesses, and often include partnership with the DoD.

Research Investments Addressing Lung Injury

Specific Problem: Current treatment for lung failure and acute respiratory distress syndrome (ARDS) is supportive and does not include specific approaches targeting anti-inflammatory and lung regeneration goals early after injury.

Approach: Stem Cells for Lung Repair

Project Title: Comprehensive Treatment of Acute Lung Failure Due to Smoke Inhalation and Burns Using Point-of-Care Mesenchymal Stem Cell Therapy

Investigation: Andriy Batchinsky, M.D., is conducting preclinical investigation at the U.S. Army Institute of Surgical Research to develop point-of-care stem cell therapy for the treatment of acute lung injury (ALI) and ARDS. Autologous and allogeneic concentrated bone marrow aspirate-derived mesenchymal stem cells are administered early after smoke inhalation and burns in clinically relevant multi-day intensive care unit models of lung failure and ARDS. This treatment is compared to standard-of-care lung protective mechanical ventilation therapy.

Research Impact: Early applications of stem cell-based therapy could treat lung failure, improve oxygenation, and prevent exacerbation of lung injury in addition to initiating lung regeneration early after injury.

Specific Problem: Pulmonary edema is a detrimental complication of burn patients with smoke inhalation leading to ARDS. The increased airway blood flow (20-fold) following smoke inhalation augments the pulmonary vascular hyperpermeability.

Approach: Airway management for burn patients with smoke inhalation

Project Title: Nebulized Epinephrine in Burn and Smoke Inhalation Injury

Investigation: Perenlei Enkhbaatar, M.D., Ph.D., at the University of Texas Medical Branch (UTMB) Galveston is leading multi-site preclinical and clinical studies on nebulized epinephrine for treatment of burn and smoke-induced ALI and ARDS. The effects of nebulized epinephrine will be compared to the standard care of therapy – nebulized albuterol. The sites include the Translational Intensive Care Unit at UTMB (conscious ovine model), U.S. Army Institute of Surgical Research (anesthetized swine model), and the Blocker Burn Unit at UTMB (clinical study).

Research Impact: Nebulized epinephrine could significantly improve pulmonary function by its dual effects: prevention of airway hyperemia and attenuation of pulmonary edema and bronchodilation. This represents a particular importance as the therapy could effectively manage "difficult" airway during the long distance transportation of wounded soldiers.

Young Investigator's Bronze Award for Oral Presentation at the 2014 Military Health System Research Symposium

Best Poster in Category at the 46th Annual (2014) American Burn Association Meeting

LTC Kevin K. Chung, M.D., FCCM, FACP
Task Area Manager, Clinical Trials in Burns and Trauma, U.S. Army Institute of Surgical Research

"Despite advances in modern medicine, nearly a third of burn patients who develop acute respiratory distress syndrome still die. Current treatment options are limited to supportive care or are overly complex for routine use. We can impact this high mortality rate through medical innovations and evidence-based medicine."

Multiple Sclerosis Research Program

VISION

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

MISSION

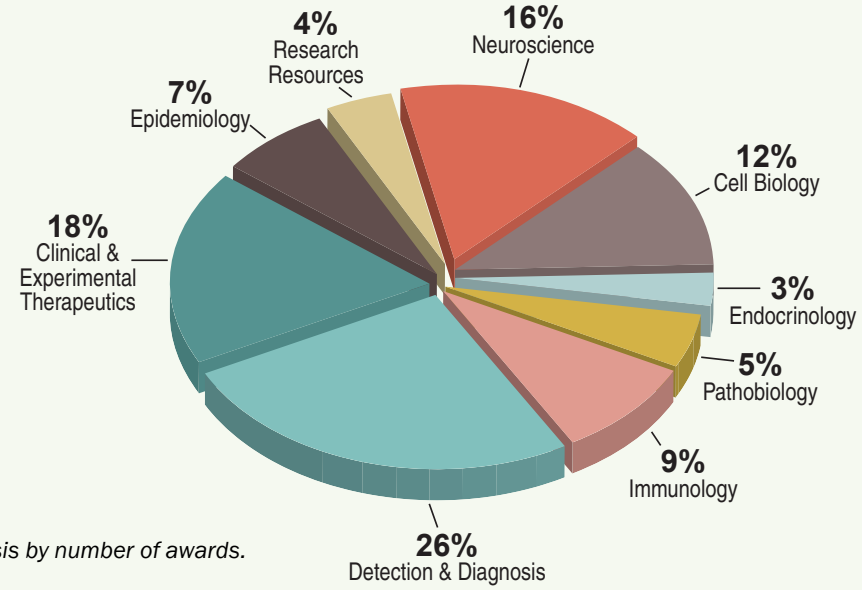
To support pioneering concepts and high impact research relevant to the prevention, etiology, pathogenesis, assessment, and treatment of multiple sclerosis

Program History

In FY09, Congress first appropriated funds for the establishment of the Multiple Sclerosis Research Program (MSRP) at the CDMRP. Annual appropriations from FY09 through FY14 total $28.1M. The MSRP has funded 57 awards through FY13, ranging from Idea Awards (22) supporting conceptually innovative, high-risk/potentially high-reward research; Synergistic Idea Awards (12) supporting multidisciplinary research collaborations; Concept Awards (14) supporting exploration of highly innovative new concepts or untested theories, and Metric Development and Validation Awards (9) supporting the development of readily accessible, cost-effective, validated analytical methods.

In FY14, the MSRP introduced a new award mechanism (Investigator-Initiated Partnership Award) to support the development of translational research collaborations among clinicians and research scientists from within and outside the Multiple Sclerosis (MS) research field to accelerate the movement of promising ideas in MS research into clinical applications.

FY09–FY13 MSRP Research Portfolio*



*Analysis by number of awards.

Timothy Coetzee, Ph.D., National Multiple Sclerosis Society, Integration Panel Member FY11–FY14, and Integration Panel Chair FY13–FY14

"Achieving the vision of a world free of MS requires innovative approaches, sufficient funding, and the collaborative efforts of researchers around the world. By helping to fund strategic research programs that address critical gaps, the MSRP is a vital partner in finding solutions that will not only end MS, but also help everyone with MS live their best lives."

Determination of the Role of Sulfatides in Remyelination and Disease Progression of Multiple Sclerosis

Maria Irene Givogri, Ph.D., University of Illinois, Chicago

Dr. Givogri

Dr. Moyano

Current methods for the diagnosis of MS can involve the evaluation of physical symptoms and imaging of the central nervous system; while blood tests can be used to rule out other diseases, none can yet confirm a diagnosis of MS. Dr. Maria Irene Givogri received an FY10 Idea Award to determine whether sulfatides – a class of glycolipids shown to be in abundance in the myelin of nerves and thought to play a major role in the upkeep of myelin – could be used to identify demyelination related to MS. Dr. Givogri, with Dr. Ana L. Moyano, Postdoctoral Associate, compared sulfatide levels in the plasma of 14 Relapsing-Remitting MS patients to 14 healthy controls and observed potentially clinically relevant results. Plasma levels of specific types of sulfatides correlated with the severity of the patient's relapse as defined by the Expanded Disability Status Scale for MS patients and also with patient age and time since last relapse. These findings suggest that plasma levels of sulfatides may reflect demyelination damage associated with MS attacks, and may serve as a potential biomarker for the diagnosis and prognosis in MS.

Inhibition of PH20 Hyaluronidase May Effectively Promote Remyelination in Multiple Sclerosis Lesions

Larry Sherman, Ph.D., Oregon Health & Science University, and Paul Weigel, Ph.D., Oklahoma Health Sciences Center

Dr. Sherman

Dr. Weigel

MS patients progressively lose the ability to remyelinate damaged myelin due, in part, to the gradual loss of oligodendrocyte progenitor cells' (OPCs) ability to mature into myelin-producing oligodendrocytes. Dr. Larry Sherman had previously discovered that a high molecular form of hyaluronan, one of the chief components of the extracellular matrix, accumulates in demyelinated lesions in MS patients. In FY09, Dr. Sherman teamed up with Dr. Paul Weigel, supported by a Synergistic Idea Award, to assess whether OPCs in demyelinating lesions, gathered from rodents with experimental autoimmune encephalomyelitis (an animal model of brain inflammation), express specific hyaluronidases, and whether the byproducts of these enzymes are implicated in inhibiting OPC maturation. Results indicated that OPCs expressed several hyaluronidases, and one, PH20, formed digestion products that inhibited OPC maturation and thus prevented remyelination. Based on these findings, Drs. Sherman and Weigel aim to identify drugs that specifically inhibit PH20 hyaluronidase activity as a potential therapeutic for promoting remyelination in MS patients.

Craig Carpenter, Paralyzed Veterans Association, MSRP Consumer Peer Reviewer, FY13

"In 2001, I was diagnosed with MS. I feel elated and honored to be given an opportunity to provide the voice and view of those with MS on grants that are focused on providing a better quality of life for people with MS. Being on the panel has been the most educational and fulfilling experience I've ever had in my life. I would recommend being a consumer reviewer to all of my fellow veterans, as you go over research applications in detail with the scientist reviewers to compare and express views from both ends of the spectrum for those affected by MS. The impact that you can provide by being on a panel as a consumer reviewer is huge. It is an effective process, and you can help those affected with MS in the future to have a better quality of life."

Charles Guttmann, M.D., Brigham and Women's Hospital, Integration Panel Member FY09–FY14

"The MSRP continues to enable original granting mechanisms promoting innovative research ideas and collaborative arrangements that complement the portfolio of private foundations and NIH funding mechanisms. In my 5 years as a member of the MSRP Integration Panel, I have had the pleasure of working side-by-side with highly motivated colleagues towards attracting relevant and potentially highly impactful research for MS. I have been gratified by the high-quality, multi-faceted response from the researcher community with its breadth of novel ideas and approaches to investigating MS."

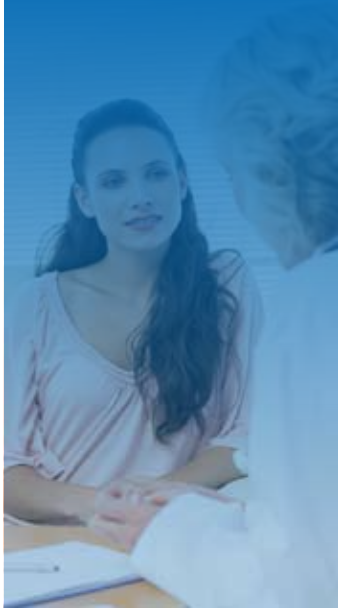
Neurofibromatosis Research Program

VISION

Decrease the clinical impact of neurofibromatosis

MISSION

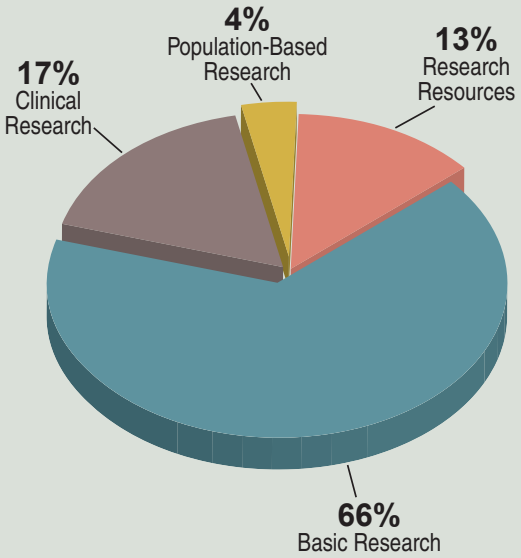
Promote research directed toward the understanding, diagnosis, and treatment of NF1, NF2, and schwannomatosis to enhance the quality of life for persons with those diseases



Program History

The Neurofibromatosis Research Program (NFRP) was established in FY96 when the efforts of NF advocates led to a congressional appropriation of $8M. Since that time, $272.85M has been appropriated to the program, including $15M in FY14. Over its 18-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 315 awards spanning basic, clinical, and population-based research.

FY96–FY13 NFRP Research Portfolio*



*Analysis by number of awards.

Frank Buono, NFRP 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 40's. The disease has affected me, and my family, in many ways – financially, emotionally, physically, and tragically. I highly recommend that individuals afflicted with this 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."

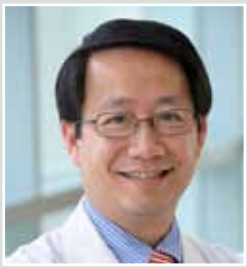
Sharon Loftspring, NFRP Consumer Advocate Peer Reviewer

"I have been active in the NF Network for over 10 years. It was through that organization that I first learned about the NFRP. Soon after, I served as a consumer reviewer of the grant proposals submitted for NF research and have continued to do so since that time. 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."

Characterization of an NF2 Model that Develops Intracranial Vestibular and Spinal Schwannomas Associated with Hearing Loss

D. Wade Clapp, M.D., Indiana University

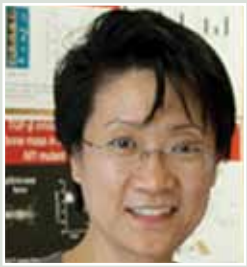
A majority of NF2 patients will eventually experience complete hearing loss due to the growth of vestibular schwannomas, non-malignant tumors in the auditory vestibular nerve. Dr. D. Wade Clapp, recipient of an FY11 Exploration – Hypothesis Development Award, has developed an NF2 mouse model that appears to form intracranial vestibular schwannomas associated with a progressive hearing loss. Dr. Clapp performed auditory brainstem response testing to determine the timeline of hearing impairment in these mice and found that although the mice have no structural defects in the inner ear (cochlea), they develop hearing loss beginning at 8 months of age, and this hearing loss grows more severe by 10 months of age. This timeline is in agreement with histological analysis of brains from these mice showing that, by 8 months, 100 percent of the mice develop vestibular schwannomas associated with the proximal spinal nerve and dorsal root ganglion responsible for transmitting nerve impulses for both balance and hearing. NF2-deficient mice also acquire spinal and peripheral schwannomas that are histologically equivalent to human schwannomas. Dr. Clapp's data suggest that this NF2 animal model will be a valuable tool with which to study disease pathogenesis and novel drugs targeting molecular pathways that are thought to be important to tumor development in NF2 and associated hearing loss.



Cell of Origin and Microenvironment Contribution in NF1-associated Peripheral Nerve Sheath Tumor Development

Lu Le, M.D., Ph.D., University of Texas Southwestern Medical Center

Dr. Lu Le has made great strides in the understanding of NF1 by determining the cell of origin for cutaneous neurofibromas to be skin-derived precursor (SKP) cells. With funding from an FY12 New Investigator Award, Dr. Le sought to determine how these SKPs interact with other cells in their microenvironment. In pursuit of his goal to identify therapeutic interventions to target these cell interactions, he developed two model systems: A novel 3D cell culture model using SKP cells and an NF-1 deficient mouse model in which SKPs give rise to plexiform neurofibromas when transplanted into a nerve environment and, with loss of tumor suppressor gene p53, MPNST. Through these models, Dr. Le and colleagues determined that G protein coupled receptor CXCR4 is highly expressed in MPNSTs compared to nonmalignant cells. Furthermore, Dr. Le found that a CXCR4 pharmacologic inhibitor, AMD3100, effectively inhibited tumor growth in vitro and in vivo. In addition, through analysis of his mouse model, he determined that BRD4, a bromodomain and extraterminal (BET) family member, was also upregulated in MPNSTs. Importantly, pharmacologic inhibition of BRD4 with compound JQ1 significantly inhibited the tumorigenesis of NF1-associated MPNSTs in this mouse model, providing strong evidence for evaluating the use of BET bromodomain inhibitors for NF1 patients who develop MPNSTs. CXCR4 and BRD4 are, therefore, two novel therapeutic targets for NF1-associated MPNSTs.



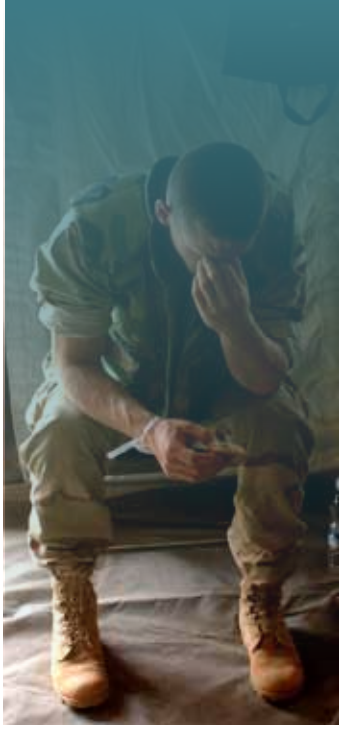
Preclinical Murine Model for Fracture Healing in NF1

Feng-Chun Yang, M.D., Ph.D., Indiana University

Individuals with NF1 carry a significant risk for both generalized and focal skeletal abnormalities including osteoporosis, dystrophic scoliosis, increased fracture rates, and failure of bone fractures to heal properly. Dr. Feng-Chun Yang has been the recipient of three separate awards to investigate the molecular mechanisms of bone abnormalities in NF1. She initially studied the mechanism underlying the pathological increase in de novo cytokine production in NF+/- mouse cells and human NF1 mast cells. She found similarities in cytokine production leading to gain in fibroblast, endothelial cell, and Schwann cell biological functions dependent on the Ras/PI3K cell signaling pathway. Next, she generated a conditional murine model in which one NF1 allele was deleted from all tissues, with the remaining allele deleted in osteoblasts only. The mice showed severe impairment of fracture healing, which was greatly improved by administration of the MEK inhibitor PD98059. Furthermore, she found elevated TGF-B1 serum levels in this mouse model and was able to use TGF-B receptor 1 inhibitor SD-208 to rescue bone mass defects and prevent tibial fracture non-union in these mice. With her NFRP funding, Dr. Yang has made significant progress in the field of NF1 research, which may lead to new therapeutic targets that will help alleviate some of the debilitating affects experienced by patients with NF1.

Neurotoxin Exposure Treatment Parkinson's Research

"Among OEF/OIF veterans, rates of PTSD, major depression, and probable TBI are relatively high, particularly when compared with general U.S. civilian population." *Invisible Wounds of War: Psychological and Cognitive Injuries, Their Consequences, and Services to Assist Recovery, RAND 2009*



Program History

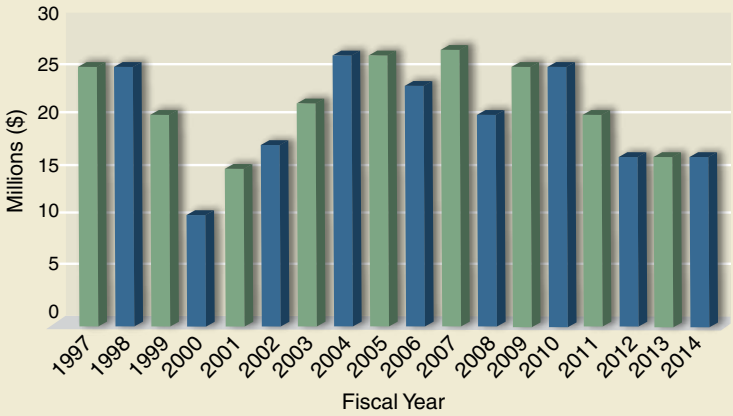
The Neurotoxin Exposure Treatment Parkinson's Research (NETPR) program began in 1997. Projects examine neurodegenerative mechanisms and compensatory effects that compromise motor, autonomic, and cognitive systems, which are characteristic alterations in Parkinson's disease (PD) patients and which also present performance and health risks for military personnel. The overall goals of the program are: 1) Develop means to correlate risk factors and dysfunction associated with PD, 2) develop means to identify risk factors for subsets of the affected population, 3) correlate clinical phenotype and molecular underpinning, and 4) develop candidate therapeutics, based on identified molecular pathway intervention points, to halt progression and extend quality of life for the at-risk population.

The program develops means to ameliorate the effect of risk factors by: 1) Preventing or delaying development of the cardinal motor signs of the conditions that compromise performance and long-term health, and 2) identification of preventions and therapeutics for currently diagnosed patients. Specific risk factors of interest include: chemical exposures, prolonged physiological stress, depression, traumatic injury to the head, disordered sleep architecture, and dysautonomia.

Amy Comstock Rick
Parkinson's Action Network CEO

"The forward-looking NETPR program advanced understanding on the biomarkers of head injury and the biochemical basis of depression. It supports research to determine the genetic basis for neurodegenerative disease risk of aging veterans as a consequence of risk factors, such as TBI and neurotoxic chemical exposure. The Parkinson's Action Network strongly supports the NETPR program, which continues to address fundamental gaps in understanding how Parkinson's disease develops, leveraging resources to discover new ways to diagnose, prevent, and treat PD for not only our Service Members but all Americans living with Parkinson's, as well as those most at risk for developing the disease in the future."

FY97–FY14 NETPR Program Funding



Neurotoxin Exposure Treatment Parkinson's Research

SERGE PRZEDBORSKI, M.D., Ph.D.; Page and William Black Professor, Neurology, Pathology & Cell Biology; Center for Parkinson's Disease and Other Movement Disorders, Columbia University

Approved treatments for PD only attenuate the symptoms of the disease, and none modify its natural course. What hampers our ability to develop effective neuroprotective therapies is our limited understanding of why and how specific neurons die in PD. In this respect, the NETPR program has been critically instrumental not only in providing funding to advance translational research in PD but also in selecting highly significant and novel projects. The NETPR program first identifies the most meritorious proposals and, among these, supports in the most meaningful manner, those projects whose thematics are most relevant to both the civilian and the military population. Moreover, this program exemplifies how the successful mixture of safe and innovative-risky research can work.

PAUL GREENGARD, Ph.D., Vincent Astor Professor, Laboratory of Molecular & Cellular Neuroscience, The Rockefeller University, Nobel Laureate, 2000 Physiology or Medicine

NETPR has been of great value in advancing the understanding of the causes and possible treatments for PD. Research activities funded by the NETPR program are amongst the very best in the field. PD is an increasingly major problem for the United States, given the aging population and the fact that aging is a major risk factor for PD. The research conducted under NETPR program is resulting in the development of a greater understanding of the etiology of Parkinsonism and has already stimulated some major novel approaches to the development of new drugs to treat this disease.

HOWARD J. FEDEROFF, M.D., Ph.D., Executive Vice President for Health Sciences, Executive Dean, School of Medicine, Georgetown University

NETPR has been a vital part of the PD research landscape. Through a very rigorous and systematic process, NETPR has sought and succeeded in funding high-impact work capable of accelerating progress towards first-ever interventions for Parkinson's patients. As a physician–scientist, I have devoted much of my research career to finding a means to modify the natural history of PD, and I could not have done so without NETPR. The program is essential to sustain the most innovative approaches that, when translated, will improve the lives of patients and families living with PD.

D. JAMES SURMEIER, Ph.D., Nathan Smith Davis Professor and Chair, Department of Physiology, Feinberg School of Medicine, Northwestern University

NETPR funding was critical to our preclinical work on the causes of PD and led to the identification of isradipine as a potential neuroprotective therapeutic. The NETPR-sponsored work motivated Phase II and now Phase III clinical trials in early stage PD patients. I enthusiastically and unequivocally endorse the NETPR program and its role in the effort to combat PD.

MICHAEL SCHWARZSCHILD, M.D., Ph.D., Professor of Neurology, Harvard Medical School; Director, Molecular Neurobiology Lab, Mass. General Institute for Neurodegenerative Disease, Mass. General Hospital; Chair, Parkinson Study Group Executive Committee

By investing in PD research at the interface of epidemiology, environmental toxicology, and neurobiology, NETPR accelerated progress of high therapeutic and military relevance. NETPR funding on purines led to current clinical research of promising neuroprotective agents, including adenosine-blocking and urate-elevating treatments, which are poised to make a major difference in the lives of PD patients. As a PD researcher and clinician dedicated to improved care for PD, I can attest to the success of the dual-purpose NETPR program. NETPR's focus on protection against environmental toxins and stressors is unique, and leverages the support of other funding agencies toward our common goals of preventing PD and its progression.

Ovarian Cancer Research Program

VISION
Eliminate ovarian cancer

MISSION
To support research to detect, diagnose, prevent, and control ovarian cancer

Did you know?

- **The DoD OCRP is the second-leading federal funding agency for ovarian cancer research in the United States.**
- **According to the World Health Organization, approximately 238,700 women were diagnosed with ovarian cancer worldwide in 2012, and 151,900 died of the disease.**
- **Ovarian cancer is the deadliest female reproductive cancer in the United States, killing approximately 14,270 women in 2014 (per the American Cancer Society).**

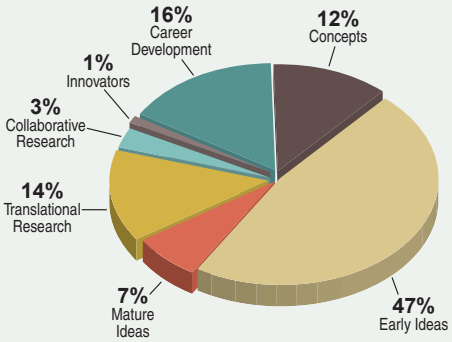
Program History

Since its inception in 1997 and over the past 17 years, the DoD Ovarian Cancer Research Program (OCRP) has had a critical role in supporting high-impact, innovative research to understand, prevent, detect, diagnose, and treat ovarian cancer. In concert with the OCRP's accomplishments, the dedicated efforts of ovarian cancer advocates to increase public awareness of and research funding for ovarian cancer have resulted in congressional appropriations totaling over $236M through FY14. As a leader in funding ovarian cancer research, the DoD OCRP invests in high-impact, cutting-edge research that fills unmet needs and pushes the field of ovarian cancer forward to eliminate this disease.

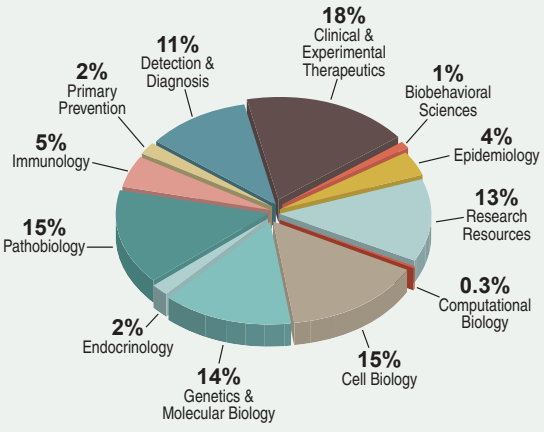
To be responsive to the needs of the ovarian cancer community, the OCRP vision is adapted yearly. The OCRP Integration Panel meets annually to deliberate the issues and concerns unique to ovarian cancer and to establish a program strategy by considering research gaps, critical research areas, and the needs of the ovarian cancer community. After evaluating the funding landscape by comparing research portfolios from federal and non-federal agencies throughout the world, the OCRP determines its program priorities, develops award mechanisms, and establishes an investment strategy to target the most critical needs along the pipeline from basic to translational to clinical research. The OCRP's annual investment strategy and associated award mechanisms provide the framework and direction necessary to most effectively invest the congressional appropriation in ovarian cancer research.

The significant impact of the OCRP can be attributed to the collective wisdom and synergistic efforts of many talented and dedicated ovarian cancer survivors (consumers), clinicians, scientists, and the military. As partners in vision setting, peer review, and programmatic review, they have shaped the OCRP by focusing on research that reflects the needs of survivors and their families, as well as the clinicians who treat them.

FY97–FY13 OCRP Development of Ideas*



FY97–FY13 OCRP Portfolio by Research Area*



*Analysis by number of awards.

Exceptionally Promising Early Results in Ovarian Cancer Research in FY14

Andrew Berchuck, M.D. – Founded the International Ovarian Cancer Association Consortium, which has published findings regarding genetic and lifestyle risks for ovarian cancer, including that tubal ligation significantly reduced risk for invasive endometrioid and clear cell ovarian cancer, with lesser reduction in risk seen for invasive serous and mucinous ovarian cancers; that low-dose regular aspirin use significantly reduced ovarian cancer risk; and that use of genital powder is not associated with ovarian cancer.

James Cooper, M.D., Ph.D. – Developing universal T cells for immunotherapy that does not require the patient to donate her own cells for her therapy; in the mouse model, these universal T cells effectively eliminated implanted human-derived ovarian cancer cells.

Validating receptor tyrosine kinase-like orphan receptor-1 as an ovarian cancer-specific target for universal T cells.

Panogiotis Konstantinopoulos, M.D., Ph.D. – Developed the BRCAness gene expression profile, which can identify tumors with the "BRCAness" phenotype (characterized by increased sensitivity to platinum analogues and PARP inhibitors as well as improved survival), and has identified that inhibition of HSP90 may improve sensitivity of these tumors to PARP inhibitors.

David Bowtell, Ph.D., and **Gillian Mitchell, Ph.D.** – Found that 44% of 141 women with nonmucinous ovarian tumors carrying BRCA1/2 mutations did not have a family history of ovarian cancer or breast cancer, changing the standard of care for genetic testing guidelines in Australia and other countries.

David Bowtell, Ph.D. – Identified that BRCA1 mutant tumors are associated with a specific molecular subtype of HGSC and have a distinct gene expression signature. By contrast, BRCA2 mutant tumors more closely resemble "wild-type" HGSC.

Nouri Neamati, Ph.D. – Preclinical tests on small-molecule gp130 inhibitor (SC144) indicate that it is able to delay tumor growth without affecting normal tissue when administered orally in a mouse model.

Eleanor Rogan, Ph.D. – Found significantly higher levels of DNA-estrogen adducts in urine samples of women with ovarian cancer compared to controls, indicative of unbalanced estrogen metabolism, and potentially useful for non-invasive detection for risk and prevention.

FISCAL YEAR 2014

In striving to achieve the vision of eliminating ovarian cancer, the DoD OCRP designed an investment strategy for FY14 that emphasizes high-impact translational research, innovation, unique partnerships, and training for talented, young investigators.

Accelerating Promising Research via the Investigator-Initiated Award

Supports research that will significantly impact ovarian cancer research and/or patient care.

Transitioning to Patient Care via the Clinical Translational Leverage Award

Dual-hatted award mechanism to accelerate successful laboratory results to the clinical setting by supporting early-phase clinical trials and correlative studies (both retrospective and prospective) to investigate high-impact research in ovarian cancer.

Supporting Innovation & Impact via the Pilot Award

Innovative, high-risk/high-reward research that may lead to critical discoveries or major advancements that will provide new paradigms, insights, technologies, or applications.

Cultivating Talented Investigators Committed to Ovarian Cancer Research via the Ovarian Cancer Academy Award

Builds a critical mass of dedicated, career ovarian cancer researchers in this unique, interactive virtual academy by providing intensive mentoring, national networking, peer support, and collaborative opportunities for junior faculty.

Facilitating Collaborative Partnerships via the Outcomes Consortium Award

Supports a multi-institutional research effort conducted by leading ovarian cancer researchers and consumer advocates that specifically focuses on identifying and understanding what is unique to long-term survivors (at least 10 years from initial diagnosis) as compared to short-term survivors.

Peer Reviewed Alzheimer's Research Program

MISSION

The PRARP seeks to 1) build an integrated program devoted to understanding the association between Traumatic Brain Injury (TBI) and Alzheimer's disease (AD), and 2) to reduce the burden on caregivers and individuals affected by TBI-AD symptoms, especially in the military community

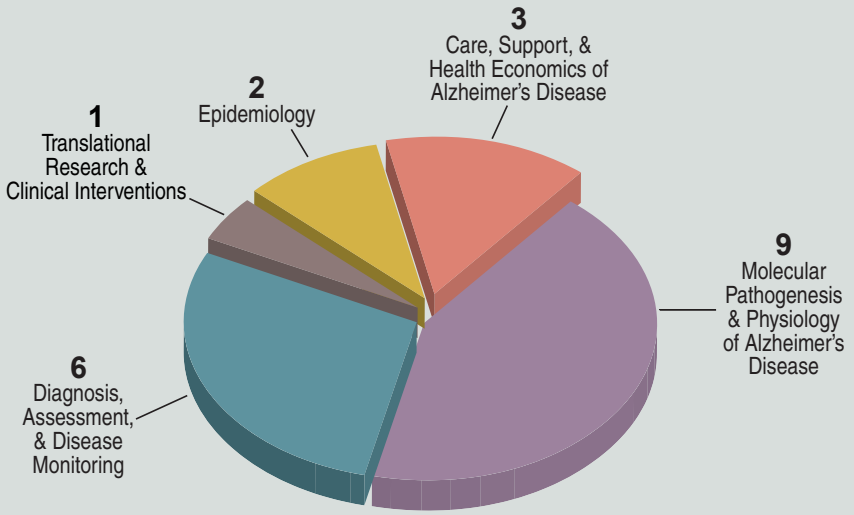
Program History

The Peer Reviewed Alzheimer's Research Program (PRARP) was established in FY11, with a congressional appropriation of $15M. Since that time, $51M has been appropriated to the program, including $12M in FY14. Over its 3-year history, the PRARP has invested in key initiatives to better understand the long-term consequences of AD. The program is also equally interested in exploring technologies, tests, interventions, epidemiological studies, or devices with the potential to benefit individuals suffering from the symptoms of TBI or AD, while reducing caregiver burden. The program's research portfolio includes 29 awards spanning biomarker development, neuropathology, and population-based research.

Maria Carrillo, Ph.D.,
Vice President, Medical & Scientific Relations at the Alzheimer's Association

"Research portfolios that investigate traumatic brain injury and post-traumatic stress disorder, and their impact on current and future military and veteran populations, will make a significant contribution to a greater understanding about Alzheimer's and other dementia. The Alzheimer's Association strongly supports this very important program that we believe will generate new insights into the causes of dementia as well as potential treatments and risk reduction strategies."

FY11–FY12 PRARP Projects by International Alzheimer's Disease Research Portfolio Ontology Criteria*



*Analysis by number of awards.

MICHAEL WEINER, M.D., THE NORTHERN CALIFORNIA INSTITUTE OF RESEARCH AND EDUCATION

Loss of consciousness and post-traumatic amnesia associated with TBIs are well recognized risk factors for neurodegenerative diseases like AD. This study evaluates Vietnam veterans with a TBI or PTSD to investigate the relationship between pathological markers of AD and cognitive decline. Dr. Michael Weiner posits that TBI and/or PTSD may lead to some of the same pathological changes seen in AD. The study takes advantage of the Alzheimer's Disease Neuroimaging Initiative (ADNI), a multi-million dollar study which developed common research protocols for researching AD. The ADNI harmonizes researchers across the nation so that results can be compared, and new insights regarding AD can be gleaned.

The Vietnam Veteran ADNI study uses many of the imaging modalities common to the original ADNI studies, including Nuclear (commonly known as PET Imaging) and MRI. The study captures data regarding psychological and cognitive measures. Biological samples are also collected (blood and cerebral spinal fluid [CSF]). The idea is that the combination of all of these measures and tests may reveal changes that no single measure by itself could characterize when collected carefully. Ultimately, the data captured from this study could reveal if and how individuals who have sustained TBIs and/or PTSD from today's conflicts are susceptible to longer-term cognitive issues from diseases such as AD. The data may provide the basis for assessing cognitive decline before it even starts in veterans who were injured.

KRISTINE YAFFE, M.D., THE NORTHERN CALIFORNIA INSTITUTE OF RESEARCH AND EDUCATION

This study examines the psychiatric symptoms (e.g., depression, anxiety) and cognitive profiles of aging veterans affected by TBI. Despite an association between TBI and increased risk of dementias such as AD, much remains unknown about the relationship between TBI and dementia.

The first part of the study is now complete. Dr. Kristine Yaffe's team surveyed nearly 300 veterans at two veteran retirement homes which were located in Washington, DC, and Northern California. The results from the study showed that 56% of those surveyed had a history of TBI. TBI was associated with psychiatric symptoms such as depression, anxiety, and PTSD. Dr. Yaffe's study has also described an association of TBI with AD symptoms such as memory issues over controls. In all cases, the association grew stronger if the TBI required hospitalization.

BRUCE LAMB, Ph.D., CLEVELAND CLINIC

The mechanisms that link TBI with neurodegenerative conditions such as AD remain a mystery. Dr. Bruce Lamb's study hypothesizes that one of the key bridges between TBI and AD is the inflammatory cascade. Dr. Lamb's study has developed sensitive measures to detect neurological changes attributed to TBI. The study uses mice prone to developing AD after TBI, and tracks two different sources of inflammation. These are the peripheral monocytes of the bloodstream, and the microglia of the brain. The extent that each plays in outcomes following TBI remains unknown.

Dr. Lamb made a recent discovery using these mice. As expected, Dr. Lamb discovered that both monocytes and microglia were present a few days after injury. What came as a surprise was that the injury continued to grow in the mice that overproduced beta-amyloid. This was also accompanied by a reduction in the immune response in these mice when compared to injured controls. The injured mice that overproduced beta-amyloid also showed worsening behavioral outcomes, including spatial working memory. This work shows that key risk factors associated with AD can modulate how the immune system functions after TBI, thus contributing to the worsening and severity of these injuries.

MICHAEL SIERKS, Ph.D., ARIZONA STATE UNIVERSITY

Novel, cost-effective strategies for detecting the early events after TBI, and the early stages of AD are sorely needed. Dr. Michael Sierks has combined two technologies, Atomic Force Microscopy and Phage Display, to generate a sensitive assay to detect signs of TBI and early neurodegeneration associated with AD. Dr. Sierks uses a virus called a bacteriophage (which only infects bacteria), to first isolate nanobodies that selectively bind toxic protein variants implicated in both AD and TBI. He has developed a simple assay to detect the toxic protein aggregates in human samples with femtomolar sensitivity. The nanobody is used to capture the target antigen, and a phage is used to amplify the detection signal. The assay is customizable for selective analysis of TBI and/or AD targets.

To date, Dr. Sierks has used the assay to detect early stages of AD in post-mortem tissue, CSF and serum samples. Dr. Sierks is currently investigating whether the assay can be used with human CSF and serum samples. If successful, the results may provide a novel, cost-effective diagnostic for TBI and AD.

Peer Reviewed Cancer Research Program

VISION

To improve quality of life by decreasing the impact of cancer on Service Members, their families, and the American public

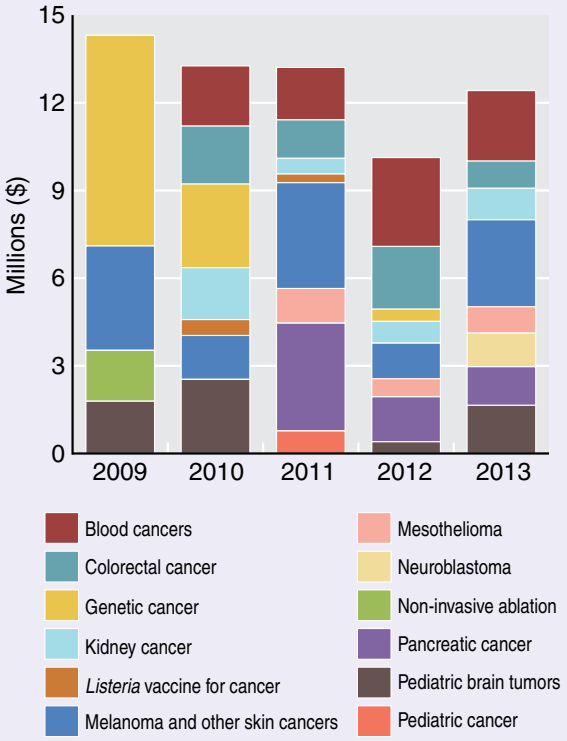
MISSION

To foster the next generation of cancer research by providing new and early-career investigators opportunities to successfully pursue high-impact research for the prevention, detection, and treatment of cancer

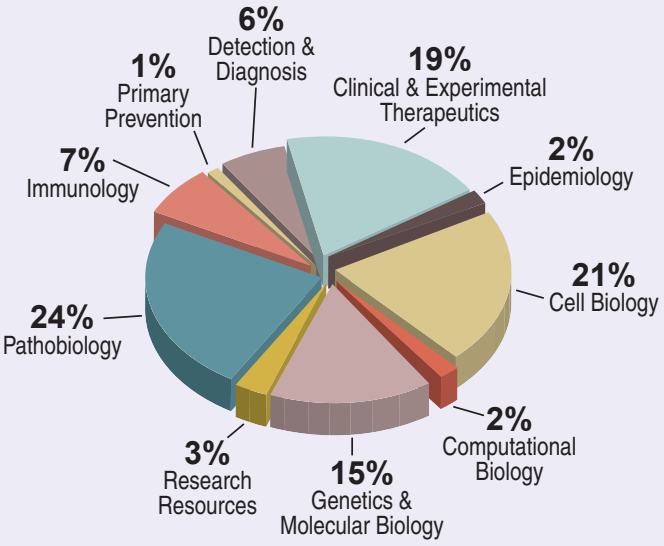
Program History

The main objective of the Peer Reviewed Cancer Research Program (PRCRP), established by U.S. Congress through an appropriation in 2009 and continuing through the current fiscal year, is to support innovative research to enhance the lives of Service Members and their families living with cancer. The Veterans Health Administration acknowledged the toll of cancer on military Service Members and their families in its National Cancer Strategy in 2003*. 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 PRCRP is charged to assess these exposures and to investigate new therapies to improve healthcare of military beneficiaries. The PRCRP manages this undertaking through creative new funding opportunities to address military risk factors. For the past two years, the PRCRP has offered a novel funding mechanism, the Idea Award with Special Focus, requiring applicants to consider the military and service as part of their research.

FY09–FY13 PRCRP Portfolio by Topic Area**



FY09–FY13 PRCRP Research Portfolio**



*VHA-Directive 2003-34
**Analysis by research dollars.

Outstanding Achievements in Cancer Research

BLOOD CANCER

Charles Lin, Ph.D., created the first comprehensive chromatin and transcriptional map of multiple myeloma to reveal asymmetry in distribution of chromatin co-activators clustered at enhancer regions containing disproportionate levels of co-activators found near key oncogenes.

COLORECTAL CANCER

Mansour Mohamadzadeh, Ph.D., found that an LTA-deficient *L.acidophilus* regulates inflammation and protects against colonic polyposis in a murine model. This discovery may lead to a preventive therapy in colorectal cancer.

GENETIC CANCER

Ann-Marie Broome, Ph.D., developed a near-infrared probe to target cells overexpressing epidermal growth factor (EGF) receptor for imaging glioblastoma brain tumors in live subjects. The lead compound selectively labeled glioblastoma-derived orthotopic brain tumors in a murine model and distinguished between different levels of expression of EGF receptor in tumors.

KIDNEY CANCER

Muneesh Tewari, M.D., Ph.D. (shown left), and Allan Pantuck, M.D., optimized a detection method for miRNA-210 and demonstrated that miRNA-210 was elevated in renal carcinoma serum samples. Further study showed that seven additional miRNAs have been identified as potential serum biomarkers and are under examination along with miRNA-120.

MELANOMA AND SKIN CANCERS

Eva Hernando, Ph.D. (shown left), and Iman Osman, M.D., performed microRNA analysis of human melanoma and found high expression of miR-30b/30d correlated with metastatic potential and shorter time to recurrence; this showed that miR-30b/30d may have a key role in metastasis.

MESOTHELIOMA

Bruce Robinson, M.D., showed that targeted removal of Treg, particularly during early tumor development, can significantly enhance anti-tumor immunity, thus delaying tumor development in a mesothelioma mouse model.

PANCREATIC CANCER

Robert Fletterick, Ph.D., screened over 5 million compounds to find the first antagonists of liver receptor homolog 1 (LRH1) that regulates functions of the liver, intestines, and pancreas, and that can be associated with tumorigenesis. The candidates identified inhibit LRH1 transcriptional activity and decrease the receptor's target gene expression.

PEDIATRIC BRAIN TUMORS

Tracy-Ann Read, Ph.D., identified CD15 as a potential biomarker for cancer stem cells in a medulloblastoma animal model and discovered that only smo/smo mice who expressed Math1, Nestin, and CD15 in medulloblastoma progressed to metastatic disease.

Lt. Col. Chad A. Hamilton, M.D., Walter Reed National Military Medical Center
FY13–FY14 Integration Panel Member

"As an active duty physician and cancer researcher, I am honored to participate in the CDMRP Peer Reviewed Cancer Research Program. The diverse members of the integration panel bring a dedication and passion to the process that ensures its integrity. I have no doubts that this program is fulfilling its charge of supporting the most promising investigators and research. In the long term, I absolutely believe that those we support today will positively impact cancer care and truly make a difference for my fellow Service Members and their families."

Elizabeth Naylor, Lymphoma Research Foundation, PRCRP Consumer Peer Reviewer

"My experience as a consumer reviewer has been incredible. It means so much to have been given a voice in something that is a part of my life. It has also been great to have the opportunity to share my story with doctors and researchers."

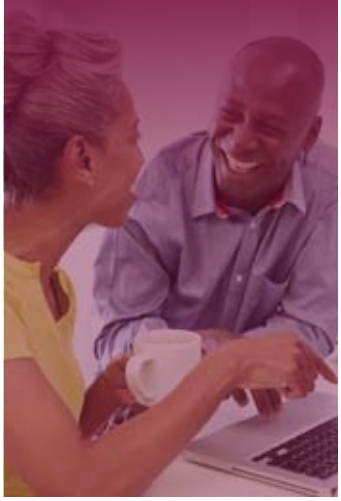
Peer Reviewed Medical Research Program

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



Program History

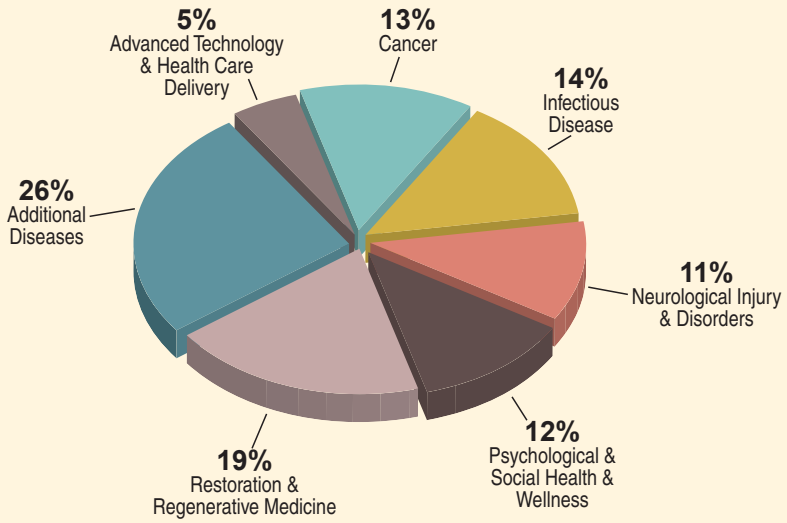
Since 1999, the Peer Reviewed Medical Research Program (PRMRP) has supported research under topic areas directed by Congress, with an underlying goal of enhancing the health and well-being of military service personnel, the veteran population, and their families. Through FY13, Congress has appropriated $644.5M, which has supported 552 research awards. The PRMRP has funded research projects in more than 100 different congressionally directed topic areas that address a wide range of fields of study including infectious diseases, cancer, neurological injury and disorders, psychological disorders, health and wellness, restoration and regenerative medicine, advanced technology, healthcare delivery, and a variety of disease conditions. The FY14 appropriation is $200M.

The PRMRP is committed to funding basic, translational, and clinical research that will strongly impact the understanding of disease and injury etiology, and the development and implementation of devices, therapies, and clinical guidance that will change the face of prevention, diagnosis, and treatment for a broad range of clinical applications.

Jon Sadler, PRMRP Epilepsy Consumer Reviewer

"I have seen people inspired when they learn they are not alone. As with any condition, one's experience can provide hope to others."

PRMRP Award Portfolio by Category and Percent Total Funding



Recent Research Accomplishments

PEDIATRIC CANCER

Aykut Uren, M.D., of Georgetown University determined the mechanism of action of two novel drug compounds and demonstrated that they are able to prevent liver and lung metastases without toxic effects in a mouse model of sarcoma.

ALCOHOLISM RESEARCH

Laura Nagy, Ph.D., of the Cleveland Clinic Foundation found that the accumulation of extracellular matrix proteins in the liver following moderate alcohol consumption can be decreased in an animal model by treatment with an adenosine 2A receptor antagonist, providing a potential new therapy for treatment of liver fibrosis associated with alcoholic liver disease.

AUTOIMMUNE DISEASE

Ashutosh Mangalam, Ph.D. (pictured left), and **Veena Taneja, Ph.D.,** of the Mayo Clinic found that dietary administration of live cultures of the gut bacterium *P. histicola* can prevent or halt disease in mouse models of both rheumatoid arthritis and multiple sclerosis.

DRUG ABUSE

Tingyu Qu, M.D., Ph.D., of the University of Chicago, Illinois developed a method to reprogram human bone marrow-derived mesenchymal stem cells to mimic adrenal chromaffin cells, and he demonstrated these chromaffin-like cells (CLCs) have an analgesic effect in an animal model, paving the way for production of autologous CLCs that may be used in chronic pain management. Dr. Qu and colleagues found that even naive mesenchymal stem cells at early passages can produce significant analgesic effects and, importantly, also inhibit tolerance development to opioid administration in an animal pain model.

2013–2014 Topic Areas

2014

- Acupuncture
- Arthritis
- Congenital Heart Disease
- Illnesses Related to Radiation Exposure
- Metabolic Disease
- Neuroprosthetics
- Psychotropic Medications
- Respiratory Health
- Segmental Bone Defects

2013 and 2014

- Chronic Migraine and Post-traumatic Headache
- DNA Vaccine Technology for Postexposure Prophylaxis
- Dystonia
- Epilepsy
- Food Allergies
- Fragile X Syndrome
- Hereditary Angioedema
- Inflammatory Bowel Disease
- Interstitial Cystitis
- Lupus
- Malaria
- Pancreatitis
- Polycystic Kidney Disease
- Post-Traumatic Osteoarthritis
- Rheumatoid Arthritis
- Tinnitus

2013

- Chronic Kidney Disease
- Composite Tissue Transplantation
- Dengue
- Hantavirus
- Leishmaniasis
- Nanomedicine for Drug Delivery Science
- Pulmonary Hypertension
- Scleroderma

Peer Reviewed Orthopaedic Research Program

VISION

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

MISSION

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

Program History

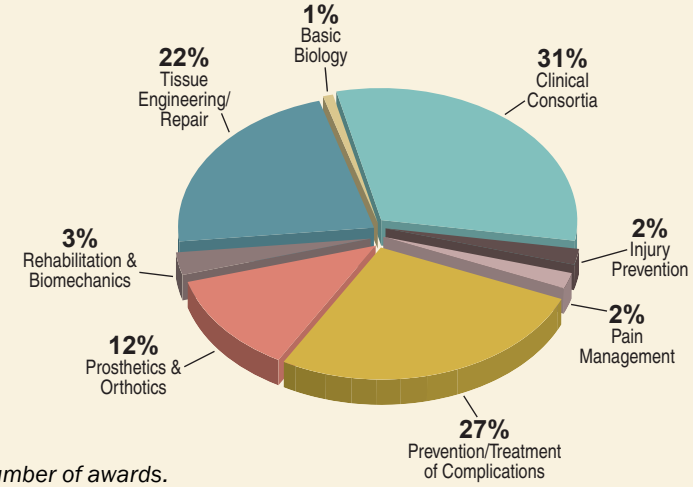
Orthopaedic injuries represent more than half of all injuries seen in combat, and are the largest source of long-term disability for returning Service Members. The impact of these injuries points to an urgent need for orthopaedic research that will provide superior medical care and treatment options for injured Service Members. Since its inception in FY09, the Peer Reviewed Orthopaedic Research Program (PRORP) has dedicated its congressional appropriations, totaling $248.5M, toward supporting military-relevant orthopaedic research.

Orthopaedic injuries sustained during combat-related activities tend to be very heterogeneous and complex in nature, involving multiple tissues such as skin, bone, muscle, cartilage, and nerves. 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, non-union of the bone, heterotopic ossification, and temporary or permanent functional muscle loss, among others. The PRORP crafts investment strategies and research portfolios to address these challenges, with the goal of helping injured Service Members achieve optimal recovery from combat-related orthopaedic injuries.

MAJ David Underwood (Ret), PRORP Consumer Reviewer

"I think it is important for those of us that have been through the process of being wounded, treated, and are living with the injuries to give back if we can to help those who cannot… I also find it all fascinating, and feel that the leaps that have been made in treatments since 2001 will benefit everyone, not just Wounded Warriors."

FY09–FY13 PRORP Research Portfolio*



*Analysis by number of awards.

Recent PRORP-supported Accomplishments Spanning the Continuum of Care:

Point of Injury

Brian Williams, M.D., Michael Gold, Ph.D., Gerald Gebhart, Ph.D., and **Chester Buckenmaier, M.D.,** developed a four-drug combination nerve block capable of providing post-traumatic acute pain relief for up to 40 hours with a single injection.

Yuki Tochigi, M.D., Ph.D., and **Jessica Goetz, Ph.D.,** created a large animal model of intra-articular fracture that mimics human fracture healing and biological responses, including development of post-traumatic osteoarthritis.

Francis Y. Lee, M.D., Ph.D., developed ready-to-use, anatomically matched, biocompatible tissue scaffolds that use growth factors to recruit autologous cells to accelerate healing of segmental bone defects.

Jason Wheeler, Ph.D., developed a biomechanical sensor system that can be incorporated into existing prosthetic socket liners to provide feedback on fit and pressure at the socket-limb interface. Dr. Wheeler is combining the sensors with novel sockets that can adjust shape to accommodate volume fluctuations of the residual limb.

David Kopperdahl, Ph.D., and **Leon Nesti, M.D., Ph.D.,** developed a "Virtual Stress Test," a three-dimensional structural model of a patient's fractured bone that allows noninvasive assessment of the strength and stability of the healing bone to assist in guiding treatment decisions and avoiding refracture.

Sameer Shah, Ph.D., designed, fabricated, and demonstrated efficacy in an animal model a device that stretches across nerve gaps and accelerates peripheral nerve regeneration through tensile loading.

Jonathan Dingwell, Ph.D., and **Jason Wilken, Ph.D.,** quantified the extent to which patients with a transtibial amputation exhibit different step-to-step control strategies from non-impaired subjects when faced with visual and physical perturbations. They are now conducting a clinical trial to determine if a virtual reality-based gait re-training program can improve step-to-step control in transtibial amputees.

Optimal Recovery & Restoration of Function

Prostate Cancer Research Program

VISION
Conquer prostate cancer

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

The PCRP-funded Prostate Cancer Clinical Trials Consortium, a collaborative group responsible for accelerating FDA approval of ZYTIGA and XTANDI, has become a limited liability company, called the Prostate Cancer Clinical Trials Consortium, LLC. The coordinating center has executed over 20 service agreements with outside sponsors and has been recognized as a qualified vendor by Novartis.

Program History

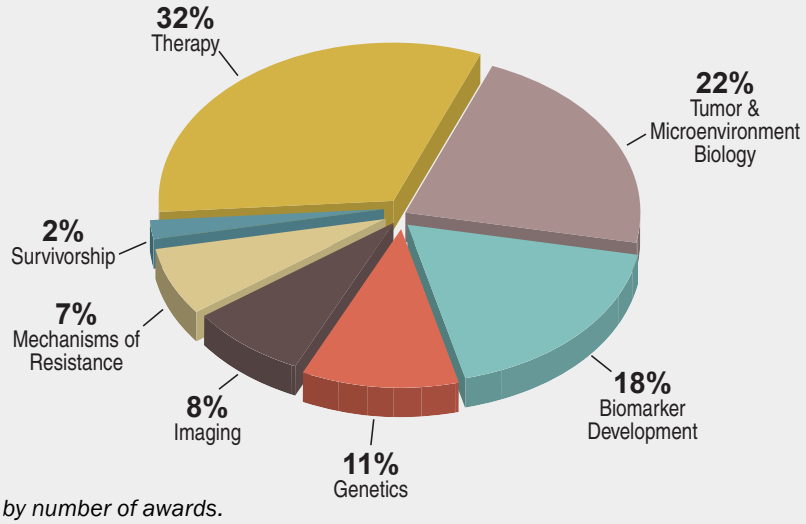
Since its inception in 1997, and over its 18-year history of congressional support totaling nearly $2.1B, the Prostate Cancer Research Program (PCRP) has changed the landscape of biomedical research and energized the prostate cancer research community to conduct high-risk research that is decidedly collaborative, innovative, and impactful, ultimately aiming to conquer the disease. The PCRP has made unprecedented inroads in supporting the development of new treatments for advanced prostate cancer, has been the leading supporter of research aimed at understanding and resolving ethnic disparities in prostate cancer incidence and mortality, and has fostered the development of over a thousand trainees and new investigators, many of whom have become leaders in cutting-edge research that is making a significant difference for millions of prostate cancer patients.

Program Portfolio

From 1997–2013, the PCRP funded 2,770 research and training awards. The supported projects range from exploratory studies that generate cutting-edge ideas to multi-institutional consortia designed to create resources that will transform prostate cancer clinical care. By achieving innovative solutions to critical challenges faced by prostate cancer 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 prostate cancer patients, as identified by the PCRP Integration Panel. The chart below shows the relative numbers of awards the program has supported in these focus areas from FY09 through FY13.

FY09–FY13 PCRP Portfolio by Focus Area*

To ensure a broad portfolio representing important areas of prostate cancer research, all PCRP-funded research must address one or more of the indicated program-specified focus areas.



*Analysis by number of awards.

From Detection to Survivorship: PCRP Research Aimed at Impacting Patients at Every Stage

The PCRP funds innovative, high-impact research focused on improving the lives of men with prostate cancer. From developing new, personalized tools capable of detecting and diagnosing the unique characteristics of each patient's prostate cancer, to finding better ways of treating the individual's specific disease, research projects funded by the PCRP are impacting patients at every stage of their battle with prostate cancer and improving their quality of life.

RISK PREDICTION

Barry Rosenstein, Ph.D., and **Harry Ostrer, M.D.,** identified novel genetic markers associated with the development of erectile dysfunction, urinary symptoms, and rectal bleeding following radiotherapy that may lead to a predictive assay to identify patients at risk for these adverse treatment outcomes.

Lorelei Mucci, Sc.D., advanced prostate cancer risk assessment with her discovery that several biomarkers (BRCA1, p63, cIAP1, and MTA1) are associated with increased risk of death.

TREATMENT

Richard Bold, M.D., showed that most prostate cancers are dependent on extracellular arginine, and that treatment with an enzyme that degrades arginine causes prostate cancer cells to die as a result of metabolic stress.

David Peace, M.D., demonstrated that prostate cancer patients treated with prostate specific antigen peptide vaccines are able to develop cytotoxic T lymphocytes targeting prostatic proteins and capable of killing tumor cells.

Steven Balk, M.D., Ph.D., demonstrated that intratumoral conversion of androgen precursors to testosterone and dihydrotestosterone is a mechanism of resistance to CYP17A1 inhibitors (e.g., ketoconazole, abiraterone) in castration-resistant prostate cancer patients.

QUALITY OF LIFE

Nathaniel Fried, Ph.D., developed a laparoscopic laser nerve imaging probe that can identify cavernous nerves during prostate cancer surgery and preserve both urinary and sexual function.

Michael Diefenbach, Ph.D., is conducting a study of men with advanced prostate cancer undergoing androgen deprivation therapy; he is using a non-pharmacological, iPod-guided paced respiration approach aimed at reducing the hot flashes these patients experience, with the goal of improving their well-being.

DETECTION AND DIAGNOSIS

Daniel Danila, M.D., demonstrated the feasibility of using molecular profiling of circulating tumor cells isolated from patient blood for sampling tumor tissue and identifying patients most likely to benefit from specific treatments.

Adam Murphy, M.D., found that reduced levels of plasma vitamin D were associated with the diagnosis of aggressive prostate cancer in men who were undergoing prostate biopsies and were associated with the diagnosis of prostate cancer among African Americans.

John Kurhanewicz, Ph.D., Donna Peehl, Ph.D., and **Sabrina Ronen, Ph.D.,** provided the first mechanistic evidence that magnetic resonance spectroscopy detection of hyperpolarized 13C lactate can be used as a prostate cancer imaging biomarker in living human tissues, critical for justification of clinical trials and appropriate biologic interpretation of patient images.

HEALTH DISPARITY

Alfred Neugut, M.D., Ph.D., found that African American men with metastatic prostate cancer were more likely to receive radiation therapy and develop spinal cord compressions than Caucasian men. He also observed that, of men who developed ureteral obstructions, African American men were more likely to undergo a nephrostomy.

Bernard Kwabi-Addo, Ph.D., provided evidence that the level of DNA methylation is higher in tumors from African American men than from Caucasian men, suggesting that epigenetic alterations may underlie racial differences in prostate cancer susceptibility.

Charnita Ziegler-Johnson, Ph.D., M.P.H., examined the geographic relationship between prostate cancer diagnosis and patient socioeconomic status, and found that prostate cancer patients living in high deprivation neighborhoods were more likely to be diagnosed with high-grade prostate cancer. This association was even greater for African Americans.

OVERARCHING CHALLENGES

To ensure that the critical needs of prostate cancer patients are being addressed by PCRP-funded research, all applicants are encouraged to focus their research efforts in one of four key areas:

- Developing better tools for early detection of clinically relevant disease
- Distinguishing aggressive from indolent disease in men newly diagnosed with prostate cancer
- Developing effective treatments and addressing mechanisms of resistance for men with high-risk or metastatic prostate cancer
- Developing strategies to optimize the physical and mental health of men with prostate cancer

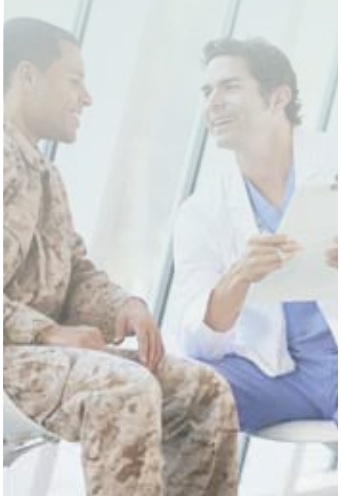
Psychological Health and Traumatic Brain Injury Research Program

VISION

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

MISSION

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



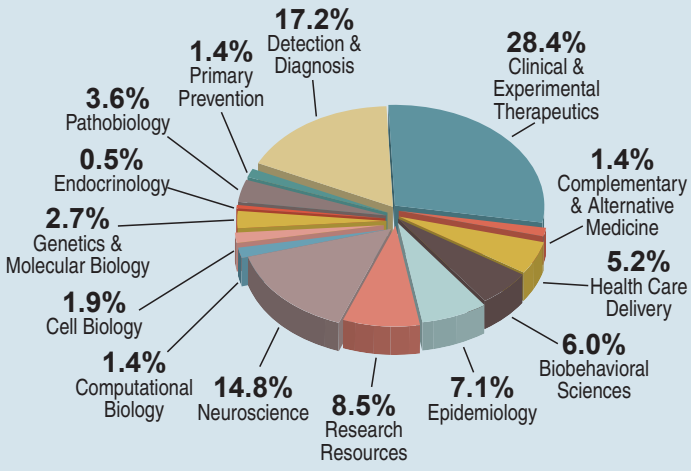
Program History

The Psychological Health and Traumatic Brain Injury Research Program (PH/TBIRP) was established by Congress in FY07 in response to the devastating impact of TBI and PH issues, including PTSD, on our deployed Service Members in Iraq and Afghanistan. Appropriations totaling $300M ($150M each for TBI and PH [including PTSD]) were assigned to the CDMRP for the purpose of soliciting and managing critical TBI- and PH-related R&D efforts to benefit Service Members, veterans, and other beneficiaries of the Military Health System.

Additional congressional appropriations for the PH/TBIRP were assigned to USAMRMC between FY09 and FY13, and a modified execution model, including assignment of program strategic oversight to USAMRMC-based Joint Programmatic Committees (JPCs) aligned with the Office of the Assistant Secretary of Defense for Health Affairs (OASD[HA]), was established. These JPCs provide recommendations to the OASD(HA) on research gaps, focus areas, and funding options for the PH/TBIRP. Operational execution management responsibilities, including development of program announcements, solicitation and review of applications, as well as full life-cycle management of awards, is supported by multiple organizations, including the CDMRP. The CDMRP-managed application review for the PH/TBIRP follows a two-tiered model, where consumer involvement continues to be a hallmark. Our nation's Wounded Warriors serve in that 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 leveraging PH/TBIRP congressional special interest funds to complement core DoD R&D efforts. For more information on this execution model, see pages 44–45 (DMRDP Execution).

To date, the CDMRP has managed 359 PH/TBIRP awards totaling over $630M 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.

FY07, FY09–FY13 PH/TBI Research Portfolio*



*Analysis by number of awards.

PH/TBIRP Recent Research Focus

Research supported by the DoD PH/TBIRP extends and complements ongoing DoD efforts towards promoting a better standard of care for PH, TBI, and related comorbidities in the areas of prevention, detection, diagnosis, treatment, and rehabilitation.

- **Novel Mechanism for Reducing Acute and Chronic Neurodegeneration After Traumatic Brain Injury**, Bruce Lyeth, Ph.D., University of California, Davis
- **Validating Biomarkers for PTSD**, Charles Marmar, M.D., New York University School of Medicine
- **Mechanism and Biomarkers of Degenerative Conditions After Repeated Mild Traumatic Brain Injury (rmTBI)**, Denes Agoston, Ph.D., Uniformed Services University of the Health Sciences
- **Harnessing Neuroplasticity to Promote Rehabilitation: CI [Constraint-Induced movement] Therapy for TBI**, Edward Taub, Ph.D., University of Alabama at Birmingham
- **A Nonpharmacologic Method for Enhancing Sleep in PTSD**, William Killgore, Ph.D., University of Arizona, Tucson
- **Uncovering Physiological Markers Linking Sleep and PTSD**, Jaques Reifman, Ph.D., TATRC
- **Comprehensive Study of Acute Effects and Recovery After Concussion**, Michael McCrea, Ph.D., Medical College of Wisconsin
- **Central Pain Mechanisms and Novel Therapeutic Strategies in a Model of Closed Head Injury**, Melanie Elliott, Ph.D., Jefferson Medical College

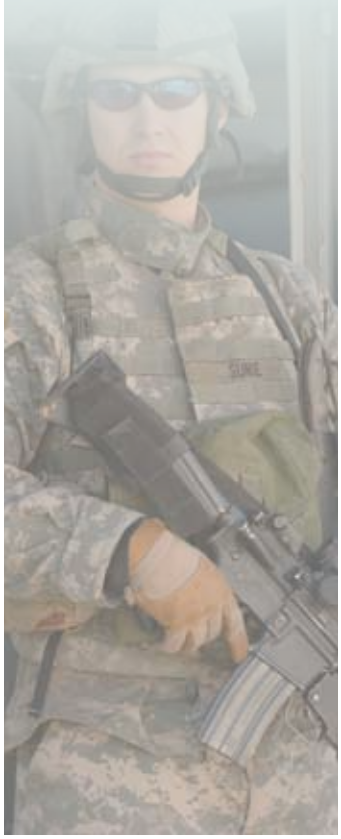
PH/TBIRP Research – Collaborating for Progress

Using PH/TBIRP funding, highly-integrated PH/TBI collaborations continue to be built with partners across the DoD, NIH, FDA, National Collegiate Athletic Association (NCAA), and more.

- **TBI Endpoints Development (TED)** – Geoffrey Manley, M.D., Ph.D., at the University of California, San Francisco, is leading a unique multi-institutional collaboration and coordination with the goal of selecting promising clinical endpoints for mild to moderate TBI that can be validated as measures for diagnostic and therapeutic TBI trials. In partnership with an array of TBI stakeholders, including patient advocacy groups and industry, and guided by FDA, the TED Research Team will leverage existing DoD, NIH, VA, and foundation-funded research networks and infrastructure, containing thousands of diverse and well-characterized military, civilian, and sports TBI subjects under study. This effort will be a major step forward in facilitating meaningful clinical trials focused on mild to moderate TBI.
- **The NCAA-DoD Grand Alliance: Concussion Assessment, Research, and Education (CARE) Consortium** – Thomas McAllister, M.D., at the Indiana University is leading the concussion research initiative of the NCAA-DoD Grand Alliance. The CARE consortium will enroll over 25,000 athletes of both sexes from 30 NCAA member institutions and Military Service Academies. This effort represents one of the most comprehensive investigations of sports-related concussion ever conducted. Athletes will wear impact sensors and undergo symptomology assessments, performance-based testing, psychological health assessments, advanced imaging, and blood/serum/saliva biomarker collection. Athletes will be baselined during the preseason, and concussion data will be collected at multiple points from the time of injury to pre/post-return to play. The aims of the CARE consortium align directly with the DoD's priorities to develop evidence-based approaches to improving the medical care, health, and welfare of our military Service Members affected by TBI. The outcomes of this effort have the potential to make an unprecedented impact on advancing the field of concussion science.

Bob Frame, COL (Ret) USA
National Returning Warriors Liaison for Vet Centers

"We are challenged by our injuries and by our return home. In our minds and our hearts, it seems like the place we want to be, to come back to. Life however, and home, has moved on ... without us. Returning is not coming back to the same place. We have to immediately understand that different is not bad, just different. Being injured makes us different to us as well as to others. This is true emotionally, mentally, spiritually, and physically. The danger is to let the injuries, the different, define us."



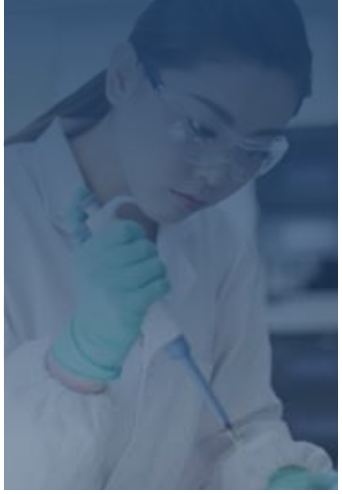
Spinal Cord Injury Research Program

VISION

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

MISSION

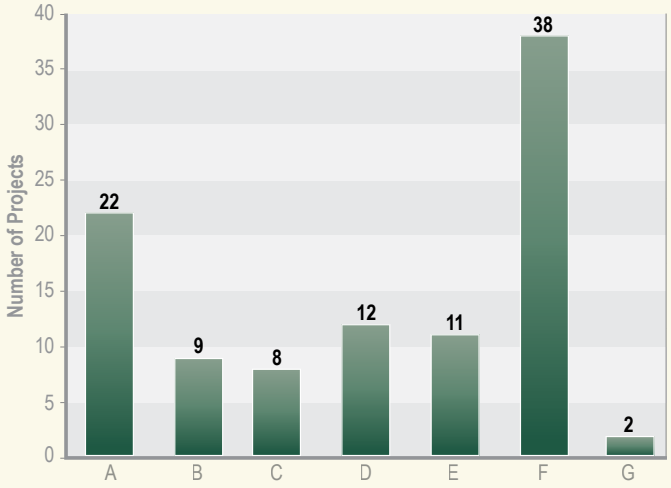
To fund research and foster collaborative environments for the development and translation of more effective strategies to improve the health and well-being of Service Members, veterans, and other individuals with spinal cord injury



Program History

Spinal cord injuries 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–FY14, Congress appropriated an additional $92.85M 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. SCIRP funding between FY09 and FY12 by areas of encouragement is shown below.

FY09–FY13 SCIRP Projects by Research Area



A = Pre-hospital, en route care, and early hospital management
B = Promising interventions, first year
C = Best practices, first year
D = Bladder, bowel, and sexual dysfunction
E = Neuropathic pain and sensory dysfunction
F = Functional deficits
G = Exoskeletal Systems

Vernon Lin, M.D., SCIRP Integration Panel Member

"SCIRP works as a catalyst. It helps identify areas of SCI research that either have tremendous clinical or scientific value, or the timing is ripe due to scientific breakthroughs and/or emerging technologies. By identifying these areas of encouragement, many outstanding researchers have now become SCI investigators who are interested in finding ways to better the lives of so many Americans with spinal cord injury and disorders."

DOUGLAS SMITH, M.D., UNIVERSITY OF PENNSYLVANIA

A major challenge to repairing an injured spinal cord is in facilitating the surviving axons to grow across a lesion site – often filled with numerous inhibitory factors – and reconnect to neural networks on the other side. Dr. Douglas Smith's laboratory has developed a neural tissue engineering strategy, based on the natural process of "stretch growth of axon tracts," to transplant living nerve constructs that may serve as a bridge across the spinal cord lesion. Dr. Smith received an FY09 Investigator-Initiated Research Award to test the feasibility of transplanting these TENGs into spinal cord-injured rats for promoting axon growth across the lesion and inducing functional recovery. TENGs were evaluated in a 5-millimeter full transection SCI rat model, which demonstrated robust survival of the transplant and evidence of nerve regeneration across the TENGs as far as 6 weeks post-transplantation. The researchers also found evidence of host (rat) axon integration with and along the TENG axons, which may lead to the reconnection of impaired neural networks.

RADI MASRI, D.D.S, Ph.D., UNIVERSITY OF MARYLAND, BALTIMORE

SCI is associated with devastating consequences, one of which is the development of severe, intractable, debilitating chronic pain. Controlling this pain is a major clinical challenge, and available medications are rarely effective. One treatment, electrical stimulation of the motor cortex (an area in the brain responsible for controlling movement), has shown great potential in reducing pain associated with SCI. Dr. Radi Masri received an FY09 Investigator-Initiated Research Award to investigate brain circuits involved in pain relief produced after electrical stimulation of the rat motor cortex. Dr. Masri and colleagues discovered a novel brain circuit that can be manipulated to manage pain following SCI. At the center of this circuit is an inhibitory nucleus called zona incerta, which is directly connected to the motor cortex. The research team found that stimulation of the motor cortex reduces pain by activating zona incerta neurons. They determined that pain relief is dependent upon stimulus frequency and duration, and can last for hours after the end of stimulation.

WEIPING QIN, M.D., Ph.D., MOUNT SINAI SCHOOL OF MEDICINE AND JAMES J. PETERS VETERANS AFFAIRS MEDICAL CENTER

SCI leads to rapid and extensive bone loss, which is associated with an elevated risk of pathologic fractures and morbidity. No practical treatment exists to prevent bone loss or promote rebuilding of bone in individuals with SCI. Dr. Weiping Qin received an FY09 Exploration – Hypothesis Development Award to investigate the potential of nandrolone, a synthetic androgen and anabolic steroid, to reduce bone loss after SCI. Dr. Qin and colleagues demonstrated in a rat model of spinal cord transection that administration of nandrolone, beginning on day 28 post-SCI, resulted in mitigation of SCI-induced bone loss by 30% at day 56. The researchers also determined that nandrolone may act through activation of an important molecular signaling pathway related to bone biology, the Wnt signaling pathway. To test a known activator of Wnt signaling for its effect on SCI-induced bone loss, SCI rats were treated with anti-sclerostin antibodies beginning 7 days post-injury. Preliminary data demonstrated that anti-sclerostin antibodies almost completely blocked bone loss in the femur, tibia, and lumbar spine. This exciting finding marks the first evidence that SCI-induced bone loss can be completely blocked.

Sherman Gillums, Paralyzed Veterans of America

"There is no better way to give back to those who saved my life, pushed me through rehabilitation, and helped me reintegrate into society than being a consumer advocate."

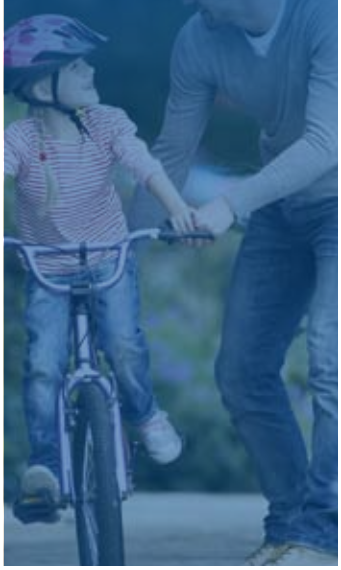
Joan Gray, Tampa General Hospital

"It was an honor to participate as a consumer advocate in the DoD SCIRP program and provide insights to the clinical investigators."

Tuberous Sclerosis Complex Research Program

VISION
To lessen the impact of TSC

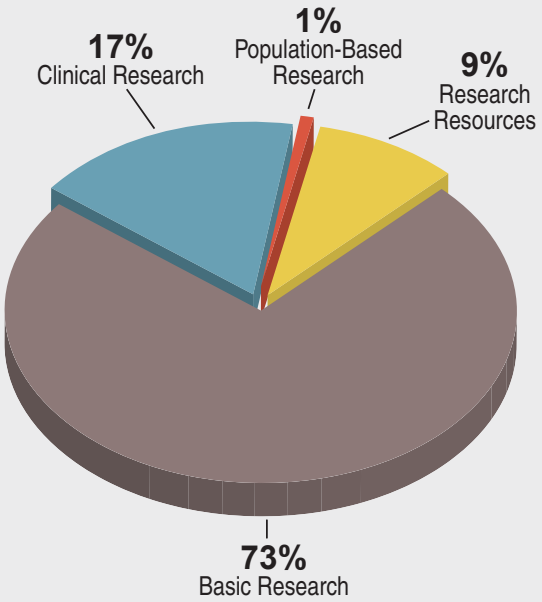
MISSION
To encourage innovative research aimed at understanding the pathogenesis and manifestations of TSC to improve the lives of individuals with TSC



Program History

The Tuberous Sclerosis Complex Research Program (TSCRP) was established in FY02 when the efforts of TSC advocates led to a congressional appropriation of $1M. Since then, a total of $53M has been appropriated to the program, including $6M in FY14. Today, the TSCRP is one of the leading sources of extramural TSC research funding in the United States. The TSCRP fills important gaps in TSC research not addressed by other funding agencies. The program's investment strategy is adapted yearly to facilitate rapid change and to better target funding to the most critical TSC research areas, thus ensuring that the program remains responsive to current needs and future opportunities. A total of 107 awards have been made through FY13, bridging basic, clinical, and population-based research.

FY02–FY06 & FY08–FY13 TSCRP Research Portfolio*



*Analysis by number of awards.

Ron Heffron, P.E., TSCRP Consumer Integration Panel Member

"My son Bao was born with TSC and associated early infantile spasms – 60-80 clusters per day. He endured four brain surgeries before his 2nd birthday. I have participated in the TSCRP as consumer reviewer for several years, and it is the single most important thing I can do for my son. This program is extremely well-run and has already resulted in clinical interventions that are vastly improving the health and quality of life of my son and so many others across the world."

Cristy Wade, TSCRP Consumer Peer Reviewer

"I feel honored to be given a chance to represent the TSC community on the selection panels to help choose the research that could have the greatest impact on our community. As a parent and volunteer, I have seen the end results of the research in the form of new treatments for the disease that have made significant impacts on the lives of those who suffer. My experience as a consumer reviewer has been educational, empowering, and very fulfilling."

Targeting Estrogen-Induced COX-2 Activity in Lymphangioleiomyomatosis

Jane Yu, Ph.D., Brigham and Women's Hospital

LAM, a rare lung disease that leads to lung destruction and respiratory failure, occurs almost exclusively in women with TSC. Dr. Jane Yu is investigating the role of estrogen in the pathogenesis of LAM and has observed that the female hormone 17-beta estradiol (E2) promotes the survival and lung metastasis of TSC2-null cells as well as increased levels of prostaglandin (PG) production, including PGE2, in these tumors. With funding from an FY11 Exploration – Hypothesis Development Award, Dr. Yu is testing her hypothesis that E2 induces COX-2 activity resulting in increased prostaglandin biosynthesis, and that COX-2 suppression will block E2-promoted lung metastasis. She found that, in TSC2-null cells, E2 increases COX-2 activity and enhances prostaglandin production in an mTORC1-independent way. Treatment of TSC2-null cells with aspirin, a COX-2 inhibitor, resulted in decreased PGE2 production and decreased cell proliferation. Moreover, aspirin treatment of a TSC2 xenograft model resulted in decreased tumor size, decreased levels of COX-2 in the tumors, and decreased urinary PGE2 levels. Furthermore, COX-2 was abundant in LAM lesions, and PGE2 serum levels were elevated in LAM patients. Dr. Yu believes that aspirin and/or other COX-1/COX-2 inhibitors may be effective in slowing the clinical progression of LAM and may be promising candidates for long-term LAM therapy.

A Mouse Model for Lymphangioleiomyomatosis

Stephen R. Hammes, M.D., Ph.D., University of Rochester

LAM is a rare lung disease in which cells contain mutations in one of the two TSC genes, TSC1 or TSC2, leading to the loss of lung function. LAM is found almost exclusively in women and has similarities with uterine leiomyomas, benign tumors of myometrial cells. Supported by an FY11 Exploration – Hypothesis Development Award, Dr. Stephen Hammes is testing the hypothesis that LAM tumors, like uterine leiomyomas, originate in the uterine myometrium and that TSC mutations provide the "additional hit" necessary to promote tumor growth and lymphatic spread to the lungs. To test this, Dr. Hammes created a mouse model for uterine leiomyomas and LAM by deleting the TSC2 gene primarily in uterine cells. All of these mice developed uterine leiomyomas that shared many characteristics with LAM tumors in humans. Uterine cell proliferation was promoted by estrogen but not progesterone in ovariectomized TSC2 null mice, mirroring the higher risk for LAM observed during pregnancy. Furthermore, inhibition of estrogen production using an aromatase inhibitor completely prevented leiomyoma formation. Finally, analysis of lung tissue in older TSC2 null mice revealed an infiltration of LAM-like, smooth muscle tumors in some of the animals, offering support for the hypothesis that LAM tumors might originate from tumors in the uterus. This new mouse model has the potential to improve our understanding of LAM and leiomyomas, and it may lead to novel therapeutic strategies for both diseases.

Defining Early Markers of Autism in Infants with TSC

Charles A. Nelson III, Ph.D., Boston Children's Hospital

Nearly 60% of children with TSC also exhibit ASD, and the diagnosis at a young age is crucial for early intervention strategies, which dramatically improve developmental outcomes. Dr. Charles Nelson, recipient of an FY10 Clinical Research Award, has sought to better define the phenotype of children with TSC and ASD in order to identify markers of ASD that could be used to predict outcomes before clinical diagnosis. In one study with children under age 4, Dr. Nelson looked at differences in neural correlates of face processing, which is thought to serve as a biomarker of ASD. Interestingly, he found that children with TSC had slower face processing than typically developing children, and face processing was particularly slow in the subset of TSC children with ASD diagnoses. In a second study, Dr. Nelson compared brain rhythms in infants with, and without, TSC. Through these analyses, he discovered that there were significant differences in electroencephalography frequencies between the two groups as early as 20–24 months of age, and he hypothesizes that frequency differences may distinguish ASD in infants with TSC. These studies may provide early markers of ASD in children with TSC prior to clinical diagnosis and allow for effective intervention strategies to improve the child's developmental outcomes.

Application of FDA-Approved Memantine and Newer NitroMemantine Derivatives to Treat Neurological Manifestations in Rodent Models of Tuberous Sclerosis Complex

Stuart Lipton, M.D., Ph.D., Sanford-Burnham Medical Research Institute

With support from an FY12 Exploration – Hypothesis Development Award, Dr. Stuart Lipton is evaluating the efficacy of the FDA-approved drug Memantine in correcting the neurological and behavioral abnormalities in a mouse model of TSC, including electrophysiological abnormalities. Memantine is currently approved for use in AD and is under investigation in clinical trials for children with autism, intellectual disabilities, and epilepsy. Dr. Lipton also plans to evaluate a novel class of Memantine derivatives called NitroMemantines.

Vision Research Program

Program History

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 Vision Research Program (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.

Capability Gaps

The goal of the VRP is to foster innovative, military-relevant research based on areas of research focus in the following areas: 1) mitigation and treatment of traumatic injuries, war-related injuries, and diseases to the ocular structure and visual system; 2) mitigation and treatment of visual dysfunction associated with TBI; 3) ocular and visual systems diagnostic capabilities and assessment strategies; 4) protection and prevention strategies; 5) vision rehabilitation strategies and quality of life measures; 6) epidemiological studies of military eye trauma and TBI-related vision dysfunction; 7) vision restoration; 8) vision care education, training, and simulation; and 9) Warfighter vision readiness and enhancement.

Robert Read and Marc Mitchell in a "one-on-one" session.

Association for Research in Vision and Ophthalmology (ARVO)

Each year, the program staff attend the annual meeting of the ARVO, the world's largest organization for eye and vision researchers. In addition to speaking at a formal session entitled "Vision Funding Opportunities," they also meet for more than 30 hours in "one-on-one" sessions with researchers to discuss the gaps and research that may be responsive to those needs.

The Horus Vision Restoration Project

A Medical Technology Enterprise Consortium is being formed to augment the current capabilities of the USAMRMC through a non-profit 501(c) (3) corporation that will have prime contractor responsibility as a consortium of small businesses, large businesses, universities, venture capital firms, and other non-profit entities. This public–private partnership will become self-sustaining after initial start-up through consortium membership fees, shared contributions, and capitalization opportunities. As a part of this consortium, vision restoration is the first formed research focus area, and this Horus project anticipates providing a prototype technology for human testing within five years that: 1) provides the ability to navigate, identify faces and objects critical to daily life, and read large print, and 2) is economically feasible. This project is named after the Eye of Horus, which is an ancient Egyptian symbol of protection, royal power, and good health.

Oversight and Collaboration

The Clinical and Rehabilitative Medicine Research Program (CRMRP) and the Vision Center of Excellence (VCE)

The **CRMRP** provides policy and process oversight, and plans, coordinates, and monitors the science and technology program focused on definitive and rehabilitative care to bring the best medical solutions and latest medical technologies to our Wounded Warriors.

The **VCE** is charged with improving the care of military personnel and veterans affected by eye injuries and diseases, including visual dysfunctions related to TBI. Research is responsible for the prevention, diagnosis, mitigation, treatment, and rehabilitation of military eye injuries, including those suffering vision damage associated with TBI and Post Traumatic Visual Syndrome.

Trauma

Treatment of Traumatic Vision Loss from Blast Injury
Tonia Rex, Ph.D., Vanderbilt University

Targeted retinal cell types that are sensitive to blast injury, how the injury is caused, how quickly the damage occurs, and in developing strategies to immediately reduce blast impact on visual function in an environment with delayed treatment availability.

Temporary Patch for Ocular Trauma
Mark Humayun, M.D., Ph.D., University of Southern California

Developed reversible glue which does not become adhesive until it is warmed and reaches body temperature.

Corneal Wound Healing
Shachar Tauber, M.D., St. John's Research Institute

Demonstrated a bandage contact lens containing therapeutic agents to sterilize the corneal wound, prevent infection, and aid in recovery; and a bio-adhesive for patients who have disrupted or missing corneal tissue.

Restoration

A Retinal Prosthetic with the Capacity to Produce Normal Vision
Sheila Nirenberg, Ph.D., Cornell University

Driving stimulators which incorporate the retina's neural code.

Miti Keratoprosthesis

Center for Ophthalmic Innovation (ONOVA)
Byron Lam, M.D., Bascom Palmer Eye Institute

Developing an "artificial tooth" keratoprosthesis to restore vision in patients with end-stage corneal scarring.

Appendix A: FY92–FY13

Table A-1. Overview of Appropriations, Applications Received, and Awards Made for FY92–FY13

Programs Managed by CDMRP[a]	Fiscal Year	Appropriations Received (in millions)	Applications Received	Applications Funded
Amyotrophic Lateral Sclerosis	2007, 2009-2013	$39.40	302	30
Autism	2007-2013	$47.40	1,081	114
Bone Marrow Failure	2008-2013	$20.15	337	46
Breast Cancer	1992-2013	$2,924.50	49,180	6,421
Chronic Myelogenous Leukemia	2002-2006	$22.05	252	61
Defense Women's Health	1995	$40.00	559	69
Deployment Related Medical	2008	$101.90	1,094	51
DoD/VA	1999-2000	$6.79	88	9
Duchenne Muscular Dystrophy	2011-2013	$10.40	53	11
Genetic Studies of Food Allergies	2009-2010	$4.38	60	9
Gulf War Illness	2006, 2008-2013	$69.00	264	73
Institutionally Based Programs	1995-2010	$486.31	306	267
Lung Cancer	2009-2013	$68.50	1,599	110
Multiple Sclerosis	2009-2013	$23.10	525	57
Myeloproliferative Disorders	2004	$4.25	18	9
National Prion	2002	$42.50	136	38
Neurofibromatosis	1996-2013	$257.85	1,306	313
Osteoporosis	1995	$5.00	105	5
Ovarian Cancer	1997-2013	$216.45	2,910	313
Peer Reviewed Cancer	2009-2013	$74.80	2,086	166
Peer Reviewed Medical	1999-2006, 2008-2013	$644.50	6,559	543
Peer Reviewed Orthopaedic	2009-2013	$218.50	734	187
Prostate Cancer	1997-2013	$1,290.00	15,441	2,765
Spinal Cord Injury	2009-2013	$97.85	593	124
Tuberous Sclerosis	2002-2006, 2008-2013	$47.00	500	107
Programs Executed on Behalf of Others[b]				
Army Rapid Innovation Fund	2011-2013	$28.84	-	12
Chiropractic Clinical Trials	2010	$8.10	5	1
Clinical Research Intramural Initiative	2013	$2.23	4	3
Defense Medical Research and Development	2010-2013	$223.99	718	128
Joint Warfighter Medical Research	2012-2013	$3.95	2	2
Psychological Health/Traumatic Brain Injury	2007, 2009-2013	$651.50	3,122	367
Vision	2013	$8.92	142	12
Total		**$7,690.11**	**90,081**	**12,423**

[a] CDMRP executed and managed the full appropriation.
[b] CDMRP assisted with execution of the specified portion of a larger appropriation(s).

Appendix B: FY13–FY14

Table B-1. FY14 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
2014	**$4.0M** for Alcohol and Substance Abuse Research	**Withholds** USAMRMC: $40,000 **Budgeted Management Costs** $316,800 (8.0%)	**Research** Budgeted Peer Reviewed Research: $3,643,200
	Total: $4.0M	**Total: $356,800**	**Total: $3,643,200**

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

Table B-2. FY13–FY14 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
2013	**$7.5M** for Amyotrophic Lateral Sclerosis Research	**Withholds** USAMRMC: $199,274 Sequestration: $595,000 Section 3001: $8,000 Section 3004: $2,000 Management Costs $576,132 (8.6%)	**Research** Therapeutic Development: $3,155,619 Therapeutic Idea: $2,963,975
	Total: $7.5M	**Total: $1,380,406**	**Total: $6,119,594**
2014	**$7.5M** for Amyotrophic Lateral Sclerosis Research	**Withholds** USAMRMC: $75,000 **Budgeted Management Costs** $587,008 (7.9%)	**Research** Budgeted Peer Reviewed Research: $6,837,992
	Total: $7.5M	**Total: $662,008**	**Total: $6,837,992**

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

Table B-3. FY13–FY14 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
2013	**$6M** for Autism Research	**Withholds** USAMRMC: $165,452 Sequestration: $476,000 Section 3001: $6,000 Section 3004: $2,000 **Management Costs** $456,868 (8.5%)	**Research** Idea Development: $2,946,453 Idea Development Multi PI: $1,073,909 Pilot Award: $873,318
	Total: $6.0M	**Total: $1,106,320**	**Total: $4,893,680**
2014	**$6M** for Autism Research	**Withholds** USAMRMC: $60,000 **Budgeted Management Costs** $473,072 (8.0%)	**Research** Budgeted Peer Reviewed Research: $5,466,928
	Total: $6.0M	**Total: $533,072**	**Total: $5,466,928**

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

Table B-4. FY13–FY14 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
2013	**$3.2M** for Bone Marrow Failure Disease Research	**Withholds** USAMRMC: $88,257 Sequestration: $254,000 Section 3001: $3,000 Section 3004: $1,000 **Management Costs** $242,625 (8.5%)	**Research** Idea Award: $113,606 Idea Development Award: $2,497,512
	Total: $3.2M	**Total: $588,882**	**Total: $2,611,118**
2014	**$3.2M** for Bone Marrow Failure Disease Research	**Withholds** USAMRMC: $32,000 **Budgeted Management Costs** $253,385 (8.0%)	**Research** Budgeted Peer Reviewed Research: $2,914,615
	Total: $3.2M	**Total: $285,385**	**Total: $2,914,615**

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

Table B-5. FY13–FY14 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
2013	**$120M** for Breast Cancer Research **$601,567** in proceeds from the Stamp Out Breast Cancer Act	**Withholds** USAMRMC: $2,361,571 Sequestration: $9,512,000 Section 3001: $119,000 Section 3004: $39,000 **Management Costs** $8,509,500 (7.8%)	**Research** Breakthrough Award Funding Level 1: $6,357,871 Breakthrough Award Funding Level 2: $21,915,290 Breakthrough Award Funding Level 3: $4,079,354 Breakthrough Award Funding Level 4: $24,192,575 Breakthrough Award Partnering PI Option: $13,926,103 Era of Hope Scholar Award: $8,664,244 Idea Expansion Award: $2,615,427 Idea Expansion Award Collaborative Option: $1,776,496 Innovator Award: $6,202,927 Postdoctoral Fellowship Award: $10,330,209
	Total: $120,601,567	**Total: $20,541,071**	**Total: $100,060,496**
2014	**$120M** for Breast Cancer Research **$497,166** in proceeds from the Stamp Out Breast Cancer Act	**Withholds** USAMRMC: $1,200,000 **Budgeted Management Costs** $9,543,773 (8.0%)	**Research** Budgeted Peer Reviewed Research: $109,753,393
	Total: $120,497,166	**Total: $10,743,773**	**Total: $109,753,393**

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

Table B-6. FY13–FY14 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
2013	**$3.2M** for Duchenne Muscular Dystrophy Research	**Withholds** USAMRMC: $88,155 Sequestration: $254,000 Section 3001: $3,000 Section 3004: $1,000 **Management Costs** $302,291 (10.6%)	**Research** Investigator-Initiated Research: $800,799 Investigator Initiated-Research – Optional Qualified Collaborator(s): $1,750,755
	Total: $3.2M	**Total: $648,446**	**Total: $2,551,554**
2014	**$3.2M** for Duchenne Muscular Dystrophy Research	**Withholds** USAMRMC: $32,000 **Budgeted Management Costs** $193,729 (6.1%)	**Budgeted Research** Budgeted Peer Reviewed Research: $2,974,271
	Total: $3.2M	**Total: $225,729**	**Total: $2,974,271**

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

Table B-7. FY13–FY14 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
2013	**$20M** for Gulf War Illness Research	**Withholds** USAMRMC: $507,531 Sequestration: $1,588,000 Section 3001: $20,000 Section 3004: $6,000 **Management Costs** $1,666,282 (9.3%)	**Research** Clinical Trial Award: $1,044,682 Consortium Award: $3,883,272 Innovative Treatment Evaluation Award: $2,930,274 Investigator-Initiated Research Award: $8,353,959
	Total: $20M	**Total: $3,787,813**	**Total: $16,212,187**
2014	**$20M** for Gulf War Illness Research	**Withholds** USAMRMC: $200,000 **Budgeted Management Costs** $1,431,689 (7.2%)	**Research** Budgeted Peer Reviewed Research: $18,368,311
	Total: $20M	**Total: $1,631,689**	**Total: $18,368,311**

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

Table B-8. FY14 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
2014	**$100M** for Joint Warfighter Medical Research	**Withholds** USAMRMC: $1,000,000 **Budgeted Management Costs** $4,633,200 (4.7%)	**Research** Budgeted Peer Reviewed Research: $94,366,800
	Total: $100M	**Total: $5,633,200**	**Total: $94,366,800**

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

Table B-9. FY13–FY14 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
2013	**$10.5M** for Lung Cancer Research	**Withholds** USAMRMC: $289,557 Sequestration: $834,000 Section 3001: $11,000 Section 3004: $3,000 **Management Costs** $760,977 (8.1%)	**Research** Concept Award: $2,800,652 Idea Development Award: $1,520,643 Career Development Award: $1,180,788 Idea Development Award – New Investigator: $1,691,520 Clinical Exploration Award: $1,107,863 Lung Cancer Biospecimen Resource Network Award: $300,000
	Total: $10.5M	**Total: $1,898,534**	**Total: $8,601,466**
2014	**$10.5M** for Lung Cancer Research	**Withholds** USAMRMC: $105,000 **Budgeted Management Costs** $825,933 (7.9%)	**Research** Budgeted Peer Reviewed Research: $9,569,067
	Total: $10.5M	**Total: $930,933**	**Total: $9,569,067**

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

Table B-10. FY14 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
2014	**$8M** for Military Burn Research	**Withholds** USAMRMC: $240,000 **Budgeted Management Costs** $620,800 (8.0%)	**Research** Budgeted Peer Reviewed Research: $7,139,200
	Total: $8M	**Total: $860,800**	**Total: $7,139,200**

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

Table B-11. FY13–FY14 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
2013	**$5.0M** for Multiple Sclerosis Research	**Withholds** USAMRMC: $15,073 Sequestration: $397,000 Section 3001: $5,000 Section 3004: $2,000 **Management Costs** $512,522 (11.2%)	**Research** Idea Award: $351,819 Idea Development Award: $3,716,586
	Total: $5.0M	**Total: $931,595**	**Total: $4,068,405**
2014	**$5M** for Multiple Sclerosis Research	**Withholds** USAMRMC: $50,000 **Budgeted Management Costs** $306,000 (5.5%)	**Research** Budgeted Peer Reviewed Research: $4,644,000
	Total: $5M	**Total: $356,000**	**Total: $4,644,000**

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

Table B-12. FY13–FY14 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
2013	**$15M** for Neurofibromatosis Research	**Withholds** USAMRMC: $417,000 Sequestration: $858,000 SBIR/STTR: $207,000 Congressional: $20,000 **Management Costs** $1,133,397 (8.4%)	**Research** Clinical Trial Award: $1,189,164 Clinical Consortium Award: $714,173 Exploration – Hypothesis Development Award: $597,250 Investigator-Initiated Research Award: $4,344,851 Investigator-Initiated Research Award – Optional Nested Postdoctoral Traineeship: $789,277 Investigator-Initiated Research Award – Optional Qualified Collaborator: $751,318 New Invesigator Award: $3,978,570
	Total: $15M	**Total: $2,635,397**	**Total: $12,364,603**
2014	**$15M** for Neurofibromatosis Research	**Withholds** USAMRMC: $450,000 **Budgeted Management Costs** $1,164,000 (8.0%)	**Research** Budgeted Peer Reviewed Research: $13,386,000
	Total: $15M	**Total: $1,614,000**	**Total: $13,386,000**

The following abbreviation is used for withholds: FFRDC – Federally Funded Research and Development Center; SBIR – Small Business Innovation Research; STTR – Small Business Technology Transfer; USAMRMC – U.S. Army Medical Research and Materiel Command
Percent of management costs=management costs/(appropriation-withholds)

Table B-13. FY14 Neurotoxin Exposure Treatment 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
2014	**$16M** for Neurotoxin Exposure Treatment Parkinson's Research	**Withholds** USAMRMC: $480,000 **Budgeted Management Costs** $1,081,968 (7.0%)	**Research** Budgeted Peer Reviewed Research: $14,438,032
	Total: $16M	**Total: $1,561,968**	**Total: $14,438,032**

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

Table B-14. FY14 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
2014	**$10M** for Orthotics and Prosthetics Outcomes Research	**Withholds** USAMRMC: $100,000 **Budgeted Management Costs** $792,000 (8.0%)	**Research** Budgeted Peer Reviewed Research: $9,108,000
	Total: $10M	**Total: $892,000**	**Total: $9,108,000**

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

Table B-15. FY13–FY14 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
2013	**$20M** for Ovarian Cancer Research Program	**Withholds** USAMRMC: $514,456 Sequestration: $1,588,000 Section 3001: $20,000 Section 3004: $6,000 **Management Costs** $1,635,709 (9.2%)	**Research** Clinical Translational Leverage Award: $1,452,609 Dean Award: $200,000 Ovarian Cancer Academy Award – Early Career Investigators: $2,555,623 Pilot Award: $7,832,130 Resource Development Award: $600,292 Synergistic Translational Leverage Award: $47,032 Teal Innovator Award: $3,548,150
	Total: $20M	**Total: $3,764,165**	**Total: $16,235,836**
2014	**$20M** for Ovarian Cancer Research	**Withholds** USAMRMC: $200,000 **Budgeted Management Costs** $1,462,463 (7.4%)	**Research** Budgeted Peer Reviewed Research: $18,337,537
	Total: $20M	**Total: $1,662,463**	**Total: $18,337,537**

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

Table B-16. FY14 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
2014	**$12M** for Peer Reviewed Alzheimer's Research	**Withholds** USAMRMC: $120,000 **Budgeted Management Costs** $950,400 (8.0%)	**Research** Budgeted Peer Reviewed Research: $10,929,600
	Total: $12M	**Total: $1,070,400**	**Total: $10,929,600**

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

Table B-17. FY13–FY14 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
2013	**$15M** for Peer Reviewed Cancer Research	**Withholds** USAMRMC: $357,662 Sequestration: $1,191,000 Section 3001: $15,000 Section 3004: $5,000 **Management Costs** $1,000,232 (7.5%)	**Research** Blood: $2,478,892 Colorectal: $932,615 Kidney: $1,077,558 Melanoma and Other Skin Cancer: $2,926,885 Mesothelioma: $900,468 Neuroblastoma: $1,151,460 Pancreatic: $1,316,078 Pediatric Brain Tumors: $1,647,150
	Total: $15M	**Total: $2,568,894**	**Total: $12,431,106**
2014	**$25M** for Peer Reviewed Cancer Research	**Withholds** USAMRMC: $250,000 **Budgeted Management Costs** $1,924,793 (7.8%)	**Research** Budgeted Peer Reviewed Research: $22,825,207
	Total: $25M	**Total: $2,174,793**	**Total: $22,825,207**

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

FY13 Peer Reviewed Cancer Research Program: The conference agreement provides $15,000,000 for a peer reviewed cancer research program that would research cancers not addressed in the breast, prostate, ovarian, and lung cancer research programs currently executed by the Department of Defense, and specifically by the USAMRMC. The funds provided are directed to be used to conduct research in the following areas: melanoma and other skin cancers, pediatric brain tumors, genetic cancer research, pancreatic cancer, kidney cancer, blood cancer, colorectal cancer, mesothelioma, neuroblastoma, and listeria vaccine for cancer. The funds provided under the Peer Reviewed Cancer Research Program shall only be used for the purposes listed above. The conferees direct the Assistant Secretary of Defense (Health Affairs) to provide a report not later than 60 days after enactment of this Act to the congressional defense committees on the status of the Peer Reviewed Cancer Research Program. For each research area, the report should include the funding amount awarded, the progress of the research, and the relevance of the research for Service Members and their families.

FY14 Peer Reviewed Cancer Research Program: The agreement provides $25,000,000 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: blood cancer, colorectal cancer, genetic cancer research, kidney cancer, listeria vaccine for cancer, melanoma and other skin cancers, mesothelioma, myeloproliferative disorders, neuroblastoma, pancreatic cancer, pediatric brain tumors, and cancers related to radiation exposure.

Table B-18. FY13–FY14 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
2013	**$50M** for Peer Reviewed Medical Research	**Withholds** USAMRMC: $1,342,181 Sequestration: $3,970,000 Section 3001: $50,000 Section 3004: $16,000 **Management Costs** $3,827,140 (8.6%)	**Research** Arthritis: $72,659 Inflammatory Bowel Disease: $119,940 Lupus: $3,815,275 Epilepsy: $908,423 Dystonia: $2,265,000 Chronic Kidney Disease: $5,986,029 Food Allergies: $1,203,750 Malaria: $1,809,757 Leishmaniasis: $3,843,906 Hereditary Angioedema: $1,044,000 Chronic Migraine and Post-Traumatic Headache: $2,190,820 Pulmonary Hypertension: $2,215,794 Hantavirus: $1,531,085 Pancreatitis: $2,417,735 Composite Tissue Transplantation: $2,319,541 Post-Traumatic Osteoarthritis: $3,525,838 Polycystic Kidney Disease: $2,383,600 Rheumatoid Arthritis: $1,164,727 Scleroderma: $1,164,800 Dengue Fever: $812,000
	Total: $50M	**Total: $9,205,321**	**Total: $40,794,679**
2014	**$200M** for Peer Reviewed Medical Research	**Withholds** USAMRMC: $2,000,000 **Budgeted Management Costs** $15,805,710 (8.0%)	**Research** Budgeted Peer Reviewed Research: $182,194,290
	Total: $200M	**Total: $17,805,710**	**Total: $182,194,290**

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

FY13 Peer Reviewed Medical Research Program: The conference agreement provides $50,000,000 for a peer reviewed medical research program. The conferees direct the Secretary of Defense, in conjunction with the Service Surgeons General, 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: chronic kidney disease, chronic migraine and post-traumatic headaches, composite tissue transplantation, dengue, DNA vaccine technology for postexposure prophylaxis, dystonia, epilepsy, food allergies, Fragile X syndrome, hantavirus, hereditary angioedema, inflammatory bowel disease, interstitial cystitis, leishmaniasis, lupus, malaria, nanomedicine for drug delivery science, pancreatitis, polycystic kidney disease, post-traumatic osteoarthritis, pulmonary hypertension, rheumatoid arthritis, scleroderma, and tinnitus. The conferees emphasize that the additional funding provided under the Peer Reviewed Medical Research Program shall be devoted only to the purposes listed above.

FY14 Peer Reviewed Medical Research Program: The agreement provides $200,000,000 for a peer reviewed medical research program. The Secretary of Defense, in conjunction with the Service Surgeons General, is directed to select medical research projects of clear scientific merit and direct relevance to military health. Research areas considered under this funding are restricted to the following areas: acupuncture, arthritis, chronic migraine and post-traumatic headache, congenital heart disease, DNA vaccine technology for postexposure prophylaxis, dystonia, epilepsy, food allergies, Fragile X syndrome, hereditary angioedema, illnesses related to radiation exposure, inflammatory bowel disease, interstitial cystitis, lupus, malaria, metabolic disease, neuroprosthetics, pancreatitis, polycystic kidney disease, post-traumatic osteoarthritis, psychotropic medications, respiratory health, rheumatoid arthritis, segmental bone defects, and tinnitus. The additional funding provided under the Peer Reviewed Medical Research Program shall be devoted only to the purposes listed above.

Table B-19. FY13–FY14 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
2013	**$30M** for Peer Reviewed Orthopedic Research	**Withholds** USAMRMC: $667,746 Sequestration: $2,382,000 Section 3001: $30,000 Section 3004: $10,000 **Management Costs** $2,318,590 (8.6%)	**Research** Clinical Trial Award: $4,132,517 Clinical Trial Development Award: $280,000 Idea Development Award: $9,870,562 Translational Research Award-Single PI Only: $9,333,376 Translational Research Partnership Award: $975,209
	Total: $30M	**Total: $5,408,336**	**Total: $24,591,664**
2014	**$30M** for Peer Reviewed Orthopedic Research	**Withholds** USAMRMC: $300,000 **Budgeted Management Costs** $2,115,804 (7.1%)	**Research** Budgeted Peer Reviewed Research: $27,584,196
	Total: $30M	**Total: $2,415,804**	**Total: $27,584,196**

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

Table B-20. FY13–FY14 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
2013	**$80M** for Prostate Cancer Research	**Withholds** USAMRMC: $1,987,975 Sequestration: $6,352,000 Section 3001: $80,000 Section 3004: $26,000 **Management Costs** $6,386,281 (8.9%)	**Research** Biomarker Development Award: $3,181,523 Clinical Consortium Award: $357,000 Clinical Consortium Award Clinical Research Site: $2,095,163 Clinical Exploration Award: $711,000 Collaborative Undergraduate HBCU Student Summer Training Program: $780,835 Exploration – Hypothesis Development Award: $5,845,461 Health Disparity Research Award: $2,480,225 Health Disparity Research Award – New Investigator Option: $3,517,674 Idea Development Award – New Investigator Option: $4,489,729 Idea Development Award Established Investigator: $17,440,502 Laboratory-Clinical Transition Award: $3,103,617 Physician Research Training Award: $3,064,960 Postdoctoral Training Award: $2,694,400 Prostate Cancer Pathology Resource Network Award: $1,611,531 Prostate Cancer Pathology Resource Network Award Coordinating Center/ Pathology Resource Network Site: $499,412 Synergistic Idea Development Award: $7,239,725 Tranformative Impact Award: $6,055,088
	Total: $80M	**Total: $14,832,256**	**Total: $65,167,845**
2014	**$80M** for Prostate Cancer Research	**Withholds** USAMRMC: $800,000 **Budgeted Management Costs** $5,951,905 (7.5%)	**Research** Budgeted Peer Reviewed Research: $73,248,095
	Total: $80M	**Total: $6,751,905**	**Total: $73,248,095**

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

Table B-21. FY13–FY14 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
2013	**$30M** for Spinal Cord Injury Research	**Withholds** USAMRMC: $818,851 Sequestration: $2,382,000 Section 3001: $30,000 Section 3004: $10,000 **Management Costs** $1,981,037 (7.4%)	**Research** Clinical Trial Award: $12,956,896 Translational Research Award: $890,653 Investigator-Initiated Research Award: $9,600,875 Qualitative Research Award: $1,055,995 Clinical Trial Award Rehabilitation Nested New Investigator Option: $273,693
	Total: $30M	**Total: $5,221,888**	**Total: $24,778,112**
2014	**$30M** for Spinal Cord Injury Research	**Withholds** USAMRMC: $300,000 **Budgeted Management Costs** $2,368,231 (8.0%)	**Research** Budgeted Peer Reviewed Research: $27,331,769
	Total: $30M	**Total: $2,668,231**	**Total: $27,331,769**

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

Table B-22. FY14 Trauma Clinical Research Repository 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
2014	**$5M** for Trauma Clinical Repository Program Research	**Withholds** USAMRMC: $50,000 **Budgeted Management Costs** $396,000 (8.0%)	**Research** Budgeted Peer Reviewed Research: $4,554,000
	Total: $5M	**Total: $446,000**	**Total: $4,554,000**

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

Table B-23. FY13–FY14 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
2013	**$6M** for Tuberous Sclerosis Complex Research	**Withholds** USAMRMC: $156,289 Sequestration: $476,000 Section 3001: $6,000 Section 3004: $2,000 **Management Costs** $1,025,750 (19.4%)	**Research** Exploration – Hypothesis Development Award: $540,789 Idea Development Award: $1,929,518 Idea Development Award – Optional Nested Postdoctoral Traineeship: $658,750 Idea Development Award – Optional Qualified Collaborator: $948,107 Pilot Clinical Trial Award: $256,797
	Total: $6M	**Total: $1,666,039**	**Total: $4,333,961**
2014	**$6M** for Tuberous Sclerosis Complex Research	**Withholds** USAMRMC: $60,000 **Budgeted Management Costs** $475,200 (8.0%)	**Research** Budgeted Peer Reviewed Research: $5,464,800
	Total: $6M	**Total: $535,200**	**Total: $5,464,800**

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

Table B-24. FY14 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
2014	**$10M** for Vision Research	**Withholds** USAMRMC: $100,000 **Budgeted Management Costs** $792,000 (8.0%)	**Research** Budgeted Peer Reviewed Research: $9,108,000
	Total: $10M	**Total: $892,000**	**Total: $9,108,000**

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

Table B-25. FY13 Army Rapid Innovation Fund
CDMRP Executed Funds, Management Costs, and Execution of Investment Strategy

Fiscal Year	CDMRP Executed Funds	Management Costs	Investment Strategy
2013	**$9.4M** for Army Rapid Innovation Fund Research	**Management Costs** $428,857 (4.6%)	**Research** Broad Agency Announcement: $8,946,768
	Total: $9.4M	**Total: $428,857**	**Total: $8,946,768**

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

Table B-26. FY13–FY14 Clinical Research Intramural Initiative Research Program
CDMRP Executed Funds, Management Costs, and Execution of Investment Strategy

Fiscal Year	CDMRP Executed Funds	Management Costs	Investment Strategy
2013	**$2.2M** for Clinical Research Intramural Initiative Research	**Management Costs** $130,889 (5.9%)	**Research** Broad Agency Announcement: $2,096,000
	Total: $2.2M	**Total: $130,889**	**Total: $2,096,000**
2014	**$5M** for Clinical Research Intramural Initiative Research	**Budgeted Management Costs** $396,000 (8.0%)	**Research** Budgeted Peer Reviewed Research: $4,554,000
	Total: $5M	**Total: $396,000**	**Total: $4,554,000**

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

Table B-27. FY13 Defense Medical Research and Development Program
CDMRP Executed Funds, Management Costs, and Execution of Investment Strategy

Fiscal Year	CDMRP Executed Funds	Management Costs	Investment Strategy
2013	**$33.7M** for Defense Medical Research and Development	**Management Costs** $3,937,583 (11.7%)	**Research** Applied Neurotrauma Research Award: $1,012,115 Applied Neurotrauma Research Award Partnering Option: $1,405,308 Applied Psychological Health Award with Clinical Trial Partnering Option: $1,144,498 Applied Research and Advanced Technology Development Award: $3,460,354 Basic Psychological Health Award: $591,000 Basic Research Award: $318,234 Broad Agency Announcement: $12,906,762 Clinical Trial Award: $1,634 DMRDP IIRA Broad Agency Announcement: $2,268,331 Intramural PTSD Investigator-Initiated Research Award: $185,414 Military Infectious Disease Applied Research Award: $2,044,320 PH/TBI IIRA Broad Agency Announcement: $2,275,264 PTSD Multidisciplinary Research Consortium Award: $2,124,495
	Total: $33.7M	**Total: $3,937,583**	**Total: $29,737,729**

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

Table B-28. FY13 Psychological Health/Traumatic Brain Injury Research Program
CDMRP Executed Funds, Management Costs, and Execution of Investment Strategy

Fiscal Year	CDMRP Executed Funds	Management Costs	Investment Strategy
2013	**$77.5M** for Psychological Health and Traumatic Brain Injury Research	**Management Costs** $3,959,905 (5.1%)	**Research** Assistive Technologies Research Award: $5,362,675 Broad Agency Announcement: $19,694,343 Chronic Effects of Neurotrauma Consortium Award: $1,034,000 Consortium to Alleviate PTSD Award: $983,952 Intramural PTSD Investigator-Initiated Research Award: $291,940 Neurosensory Research Award: $12,432,929 PH/TBI IIRA Broad Agency Announcement: $782,338 Psychological Health Award Applied/ Combined Research: $10,368,547 Traumatic Brain Injury Endpoints Development Award: $5,000,000 Traumatic Brain Injury Research Award: $11,034,591 VRP Hypothesis Development Award: $6,500,462
	Total: $77.5M	**Total: $3,959,905**	**Total: $73,485,777**

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

Table B-29. FY13 Joint Warfighter Medical Research Program
CDMRP Executed Funds, Management Costs, and Execution of Investment Strategy

Fiscal Year	CDMRP Executed Funds	Management Costs	Investment Strategy
2013	**$3.95M** for Joint Warfighter Medical Research	**Management Costs** $813,327 (20.6%)	**Research** Idea Award: $3,139,754
	Total: $3.95M	**Total: $813,327**	**Total: $3,139,754**

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

Table B-30. FY13 Vision Research Program
CDMRP Executed Funds, Management Costs, and Execution of Investment Strategy

Fiscal Year	CDMRP Executed Funds	Management Costs	Investment Strategy
2013	**$8.9M** for Vision Research	**Management Costs** $226,296 (2.6%)	**Research** Translational Research Award: $8,690,674
	Total: $8.9M	**Total: $226,296**	**Total: $8,690,674**

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

Appendix C: Breast Cancer Research Semipostal Awards FY99–FY13

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

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

Fiscal Year	Principal Investigator	Amount	Institution	Proposal Title
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
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

[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.

Fiscal Year	Principal Investigator	Amount	Institution	Proposal Title
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
FY11	Minn	$399,942	University of Pennsylvania	Regulation of Metastasis and DNA Damage Resistance Pathways by Transposable Elements
	Wang	$409,693	Baylor College of Medicine	Copy Number Signature of Recurrent Gene Fusions Reveals Potential Drug Targets in Invasive Breast Cancer
	Gonzalo Hervas	$58,975[10]	St. Louis University	Stabilization of 53BP1 in Triple-Negative and BRCA-Deficient Breast Tumors: A Novel Therapeutic Strategy
FY12	Yang	$465,000	University of California, San Diego	Regulation of Breast Cancer Stem Cell by Tissue Rigidity
	Giancotti	$174,837[11]	Memorial Sloan Kettering Cancer Center	Autophagy and TGF-Beta Antagonist Signaling in Breast Cancer Dormancy at Premetastatic Sites
FY13	Rubin	$457,075	University of California, Santa Cruz	Inhibition of Retinoblastoma Protein Inhibition
	Luke	$96,992[12]	University of Texas at Austin	Noninvasive Label-Free Detection of Micrometastases in the Lymphatics with Ultrasound-Guided Photoacoustic Imaging

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

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

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

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

[10]Total award amount was $744,661; remaining funds were from the FY11 BCRP.

[11]Total award amount was $331,449; remaining funds were from the FY12 BCRP.

[12]Total award amount was $497,288; remaining funds were from the FY13 BCRP.

Appendix D: Acronyms

3D ..... three-dimensional
AD ..... Alzheimer's disease
ADNI ..... Alzheimer's Disease Neuroimaging Initiative
ADPKD ..... autosomal dominant polycystic kidney disease
ALI ..... acute lung injury
ALS ..... amyotrophic lateral sclerosis
ALSRP ..... Amyotrophic Lateral Sclerosis Research Program
AR ..... androgen receptor
ARDS ..... acute respiratory distress syndrome
ARP ..... Autism Research Program
ARVO .... Association for Research in Vision and Ophthalmology
ASARP ..... Alcohol and Substance Abuse Research Program
ASD ..... autism spectrum disorder
BAA ..... Broad Agency Announcement
BADER ..... Bridging Advanced Developments for Exceptional Rehabilitation
BCRP ..... Breast Cancer Research Program
BCRS ..... Breast Cancer Research Semipostal
BET ..... bromodomain and extraterminal
BIgG ..... bovine milk immunoglobulin
BMD ..... Becker muscular dystrophy
BMFRP ..... Bone Marrow Failure Research Program
CAP ..... Consortium to Alleviate PTSD
CAPP-Seq .. Cancer Personalized Profiling by Deep Sequencing
CARE ..... Concussion Assessment, Research, and Education
CCCRP ..... Combat Casualty Care Research Program
CDC ..... Centers for Disease Control and Prevention
CDMRP .. Congressionally Directed Medical Research Programs
CENC ..... Chronic Effects of Neurotrauma Consortium
CLC ..... chromaffin-like cell
COX-2 ..... cyclooxygenase-2
CRMRP ..... Clinical and Rehabilitative Medicine Research Program
CSF ..... cerebral spinal fluid
dAIH ..... daily mild intermittent hypoxia
DANA ..... Defense Automated Neurobehavioural Assessment
DECAMP ..... Detection of Early Lung Cancer Among Military Personnel
DHA ..... docosahexaenoic acid
DMD ..... Duchenne Muscular Dystrophy
DMDRP ..... Duchenne Muscular Dystrophy Research Program
DMRDP ..... Defense Medical Research and Development Program
DoD ..... U.S. Department of Defense
E2 ..... 17-beta estradiol
eBRAP ..... Electronic Biomedical Research Application Portal
ECI ..... Early-Career Investigator
EGF ..... epidermal growth factor
EGFR ..... epidermal growth factor receptor
EGS ..... Electronic Grants System
ES-MN ..... embryonic stem motor neuron
ETEC ..... enterotoxigenic *Escherichia coli*
FAK ..... focal adhesion kinase
FDA ..... U.S. Food and Drug Administration
FFRDC .... Federally Funded Research and Development Center
FGFR2 ..... fibroblast growth factor receptor 2
FITBIR ..... Federal Interagency TBI Research
fMRI ..... functional magnetic resonance imaging
FOXP3 ..... forkhead box protein 3
FY ..... fiscal year
GWI ..... Gulf War Illness
GWIC ..... Gulf War Illness Consortia
GWIRP ..... Gulf War Illness Research Program
HER2 ..... human epidermal growth factor receptor 2
HGSC ..... high-grade serous carcinoma
HPA ..... hypothalamic-pituitary-adrenal
HPG ..... hypothalamic-pituitary-gonadal axis
HSPC ..... hematopoietic stem/progenitor cells
INTRuST ..... INjury and TRaumatic STress Consortium
IOM ..... Institute of Medicine
IPT ..... Integrated Product Team
JPC ..... Joint Program Committee

JWMRP ..... Joint Warfighter Medical Research Program
LAM ..... lymphangioleiomyomatosis
LCRP ..... Lung Cancer Research Program
LRH1 ..... liver receptor homolog 1
LTA ..... lipoteichoic acid
M ..... Million
MACE ..... Military Acute Concussion Evaluation
MBRP ..... Military Burn Research Program
MDCC ..... Muscular Dystrophy Coordinating Committee
MIDRP ..... Military Infectious Diseases Research Program
MN ..... motor neuron
MOMRP ..... Military Operational Medicine Research Program
MPNST ..... malignant peripheral nerve sheath tumor
MRI ..... magnetic resonance imaging
MS ..... Multiple Sclerosis
MSRP ..... Multiple Sclerosis Research Program
mTBI ..... mild TBI
NCAA ..... National Collegiate Athletic Association
NETPR .. Neurotoxin Exposure Treatment Parkinson's Research
NF ..... neurofibromatosis
NF1/2 ..... NF type 1/2
NFCTC ..... Neurofibromatosis Clinical Trials Consortium
NFRP ..... Neurofibromatosis Research Program
NIH ..... National Institutes of Health
NPCs ..... neural precursor cells
NSCLC ..... non-small-cell lung carcinoma
OASD[HA] ..... Office of the Assistant Secretary of Defense for Health Affairs
OCCA ..... Ovarian Cancer Consortium Award
OCRP ..... Ovarian Cancer Research Program
OPC ..... oligodendrocyte progenitor cell
ORP ..... Office of Research Protections
OT ..... oxytocin
PARP-1 ..... poly(ADP-ribose) polymerase 1
PCBN ..... Prostate Cancer Biorepository Network
PCCTC ..... Prostate Cancer Clinical Trials Consortium
PCr ..... phosphocreatine
PCRP ..... Prostate Cancer Research Program
PD ..... Parkinson's disease
PG ..... prostaglandin
PGAM1 ..... phosphoglycerate mutase 1
PH ..... psychological health
PH/TBIRP ..... Psychological Health and Traumatic Brain Injury Research Program
PI ..... Principal Investigator
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
PPI ..... protein–protein interactions
PTEN ..... phosphatase and tensin homolog
PTSD ..... post-traumatic stress disorder
R&D ..... research and development
RDTE ..... Research, Development, Testing, and Evaluation
rmTBI ..... Repeated Mild Traumatic Brain Injury
RNAi ..... RNA interference
SBIR ..... Small Business Innovation Research
SCI ..... spinal cord injury
SCIRP ..... Spinal Cord Injury Research Program
shRNA ..... small hairpin RNA
SKP ..... skin-derived precursor
SNPs ..... single-nucleotide polymorphisms
SO ..... Science Officer
SOD1 ..... superoxide dismutase-1
STIC ..... serous tubal intraepithelial carcinoma
STIL ..... serous tubal intraepithelial lesion
STRONG STAR ..... South Texas Research Organizational Network Guiding Studies on Trauma and Resilience
SRY ..... sex-determining region Y
STTR ..... Small Business Technology Transfer
SUD ..... substance use disorder
TATRC ..... Telemedicine and Advanced Technology Research Center
TBI ..... Traumatic Brain Injury
TED ..... TBI Endpoints Development
TENG ..... tissue-engineered nerve graft
TGFbeta-1 ..... transforming growth factor beta 1
Treg ..... T cells
TRL ..... technology-readiness level
TSC ..... Tuberous Sclerosis Complex
TSCRP ..... Tuberous Sclerosis Complex Research Program
TTIP ..... Treatments for Tissue Injury Portfolio
USAMRAA ..... U.S. Army Medical Research Acquisition Activity
USAMRMC ..... U.S. Army Medical Research and Materiel Command
UTMB ..... University of Texas Medical Branch
VA ..... U.S. Department of Veterans Affairs
VCE ..... Vision Center of Excellence
VRP ..... Vision Research Program

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

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