OFFICE OF THE UNDER SECRETARY OF DEFENSE
4000 DEFENSE PENTAGON
WASHINGTON, DC 20301-4000

PERSONNEL AND
READINESS

FEB 24 2017

The Honorable William M. "Mac" Thornberry
Chairman
Committee on Armed Services
U.S. House of Representatives
Washington, DC 20515

Dear Mr. Chairman:

The enclosed report is in response to Senate Report 113-211, page 252, which accompanied H.R. 4870, the Department of Defense Appropriations Bill, 2015, requesting a report on the breakdown of funding in the Peer Reviewed Medical Research Program (PRMRP)/Congressionally Directed Medical Research Program (CDMRP) between basic and advanced research for the funding added by Congress. Research programs managed by the PRMRP/CDMRP establish annual investment strategies that target the type of research that not only will meet each program's vision and goals, but fill gaps in the research field and funding landscape.

The PRMRP/CDMRP's programs are able to shift the focus of their award mechanisms as needed to target the most critical needs along the pipeline of translating basic research to the clinic. More than one-quarter of the CDMRP's awards include a clinical trial, so it is clear that supporting advanced research is a priority of the CDMRP. A similar letter is being sent to the other Congressional defense committees. Thank you for your interest in the health and well-being of our Service members, veterans, and their families.

Sincerely,

AM Kurta

A. M. Kurta
Performing the Duties of the Under Secretary of
Defense for Personnel and Readiness

Enclosure:
As stated

cc:
The Honorable Adam Smith
Ranking Member

OFFICE OF THE UNDER SECRETARY OF DEFENSE
4000 DEFENSE PENTAGON
WASHINGTON, DC 20301-4000

PERSONNEL AND
READINESS

FEB 24 2017

The Honorable John McCain
Chairman
Committee on Armed Services
United States Senate
Washington, DC 20510

Dear Mr. Chairman:

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Sincerely,

AMKurta

A. M. Kurta
Performing the Duties of the Under Secretary of
Defense for Personnel and Readiness

Enclosure:
As stated

cc:
The Honorable Jack Reed
Ranking Member

OFFICE OF THE UNDER SECRETARY OF DEFENSE
4000 DEFENSE PENTAGON
WASHINGTON, DC 20301-4000

PERSONNEL AND
READINESS

FEB 24 2017

The Honorable Thad Cochran
Chairman
Subcommittee on Defense
Committee on Appropriations
United States Senate
Washington, DC 20510

Dear Mr. Chairman:

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Sincerely,

A. M. Kurta
Performing the Duties of the Under Secretary of
Defense for Personnel and Readiness

Enclosure:
As stated

cc:
The Honorable Richard J. Durbin
Vice Chairman

OFFICE OF THE UNDER SECRETARY OF DEFENSE
4000 DEFENSE PENTAGON
WASHINGTON, DC 20301-4000

PERSONNEL AND
READINESS

FEB 24 2017

The Honorable Kay Granger
Chairwoman
Subcommittee on Defense
Committee on Appropriations
U.S. House of Representatives
Washington, DC 20515

Dear Madam Chairwoman:

The enclosed report is in response to Senate Report 113-211, page 252, which accompanied H.R. 4870, the Department of Defense Appropriations Bill, 2015, requesting a report on the breakdown of funding in the Peer Reviewed Medical Research Program (PRMRP)/Congressionally Directed Medical Research Program (CDMRP) between basic and advanced research for the funding added by Congress. Research programs managed by the PRMRP/CDMRP establish annual investment strategies that target the type of research that not only will meet each program's vision and goals, but fill gaps in the research field and funding landscape.

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A. M. Kurta
Performing the Duties of the Under Secretary of
Defense for Personnel and Readiness

Enclosure:
As stated

cc:
The Honorable Peter J. Visclosky
Ranking Member

REPORT IN RESPONSE TO SENATE REPORT 113-211, PAGE 252, ACCOMPANYING H.R. 4870, DEPARTMENT OF DEFENSE APPROPRIATIONS ACT, 2015

"PEER REVIEWED MEDICAL RESEARCH PROGRAM / CONGRESSIONALLY DIRECTED MEDICAL RESEARCH PROGRAMS"

SUBMITTED BY THE OFFICE OF THE ASSISTANT SECRETARY OF DEFENSE FOR HEALTH AFFAIRS

SUPPORTED BY THE U.S. ARMY MEDICAL RESEARCH AND MATERIEL COMMAND

December 2016

The estimated cost of this report or study for the Department of Defense (DoD) is approximately $20,000 in Fiscal Years 2015 – 2016. This includes $19,000 in expenses and $1,220 in DoD labor.
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Peer Reviewed Medical Research Program/Congressionally Directed Medical Research Programs
Fiscal Year 2015 Report to Congress

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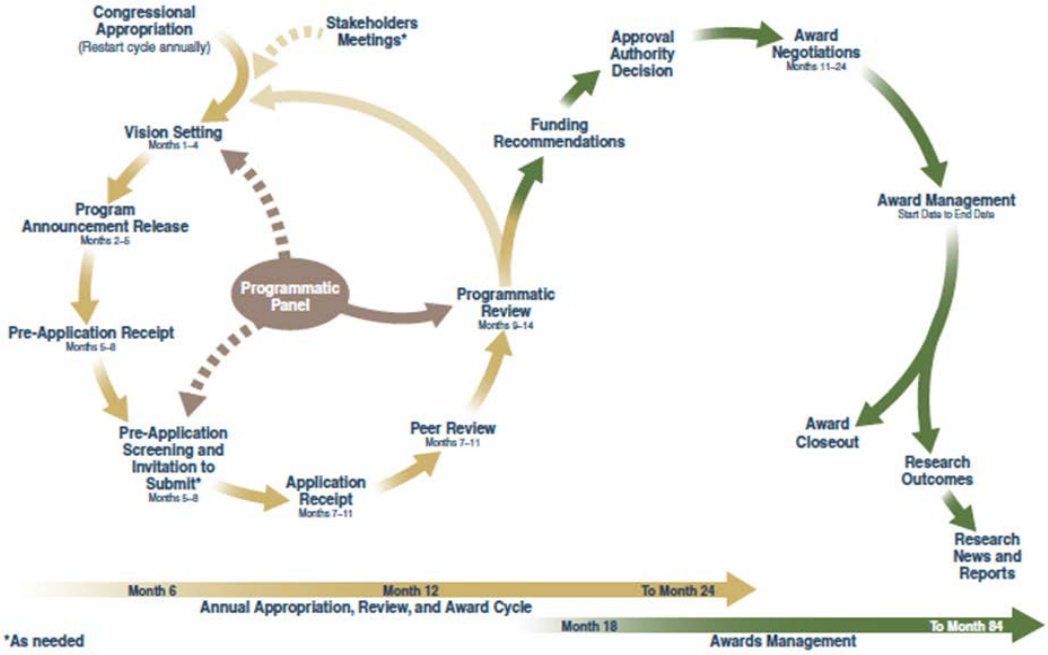
PURPOSE OF REPORT

Senate Report 113-211, page 252, accompanying H.R. 4870, the Department of Defense Appropriations Bill, 2015, requested "a report to the congressional defense committees within 180 days of enactment of this Act on the breakdown of funding in the Peer Reviewed Medical Research Program/ Congressionally Directed Medical Research program between basic and advanced research." Specifically, Senate Report 113-211 stated that the Committee "remains supportive of the medical research being conducted by the Department that yields medical breakthroughs for Service members and often translates to the civilian population, as well."

BACKGROUND

The Congressionally Directed Medical Research Program (CDMRP) is a program execution and management agent for multiple Congressional Special Interest medical research programs, and is responsible for program planning, coordination, integration, budgeting, evaluation, administration, and reporting for each program. The CDMRP uses a flexible execution cycle that is designed to tailor each program's research portfolio to the often rapidly changing knowledge gaps and discoveries within each relevant research field. The cycle follows the appropriations from program initiation to award closure and includes the receipt of annual Congressional appropriations, stakeholder meetings for new research programs, vision setting, release of funding opportunities soliciting research applications, pre-application screening and invitation to submit full applications, full application receipt and review, recommendation of applications for funding, and oversight of research awards (Figure 1).

Figure 1. The Program Execution Cycle



At the center of the program execution cycle is a two-tier review process. The two-tier review process includes a scientific peer review and a programmatic review, which are critical to ensuring that each of the CDMRP research portfolios reflects both the most meritorious science

and the most programmatically relevant research. This process was adopted from the recommendations set forth in 1993 by the National Academy of Medicine.[1] Scientifically sound applications that best meet each program's goals are recommended to the Commanding General, U.S. Army Medical Research and Materiel Command (USAMRMC) and the Director of the Defense Health Agency Research, Development and Acquisition Directorate for funding. Once approved, funding notifications are sent to investigators; awards are typically made in the form of one- to five-year assistance agreements and assigned to the CDMRP staff for full-cycle oversight of research progress and outcomes. The CDMRP ensures the integrity of the review process and provides transparency by publishing information on funded applications, programmatic panel members, ad hoc programmatic reviewers, peer review panelists, abstracts, and research accomplishments on the CDMRP website (http://cdmrp.army.mil). The programs that comprise the CDMRP are scientifically sound, innovative, and responsive to Congressional intent and the needs of the military and the public. The USAMRMC and the CDMRP have been praised by the National Academy of Medicine, which issued a report stating that it was favorably impressed with the processes implemented by the CDMRP and that it supported CDMRP's continuation.[2]

Each CDMRP program is guided by a programmatic panel comprised of scientists and clinicians with renowned expertise in relevant areas of research and medicine, consumers from advocacy communities, and members of the military and other Government organizations.[3] Each program has a vision statement that reflects its overarching goals of ending or curing its respective disease, condition, or injury, ameliorating the consequences, and/or having a major impact on the quality of life of the survivors. On an annual basis, each programmatic panel examines its program's goals and vision statement, and refines them as appropriate to reflect the current state of science and medicine. Following a comprehensive review of the program's portfolio, the present-day research and funding landscapes, and potential directions, the investment strategy for the program is developed, as well as the award mechanisms that will be offered as funding opportunities to fulfill the investment strategy.

Establishment of a program's goals, vision statement, and investment strategy leads to the development of funding opportunities requesting medical research applications to address the goals of the program. Funding opportunities are published and advertised broadly to solicit research applications aimed at making scientific advances that have a significant impact for the individuals affected by the relevant diseases, injuries, and conditions. The CDMRP's diverse funding opportunities enable and support a broad range of research, including exploring early-stage concepts, developing a foundation to understand disease biology and etiology, investigating therapeutic efficacy in disease models, advancing technological innovations, and conducting clinical trials and studies in human populations.

The current report covering Fiscal Year (FY) 2015 provides a summary of the breakdown of funding invested by the CDMRP along the continuum of basic, translational (applied), and advanced research.

CDMRP FUNDING OPPORTUNITIES BY TYPE OF RESEARCH

As noted above, each of the programs managed by the CDMRP develops a research investment strategy that is responsive to the dynamic changes in its respective field and is adapted yearly to meet emerging needs of patient and research communities, fill gaps in research, and address other barriers to progress. The programmatic panel of each program recommends how to implement the research investment strategy through specific and clearly defined award mechanisms designed to address research focus areas. The types of research supported by the CDMRP's award mechanisms range from early-stage concepts and ideas at the basic research level, to translational projects at the applied research level, to advanced research supporting clinical trials. Thus, the CDMRP enables investigators to submit applications at every stage of idea and research development through the award mechanisms offered across its different programs. Since its inception, the CDMRP has developed and released more than 975 Program Announcements to the public as funding opportunities for the solicitation of research proposals focused on the specific goals of each research program.

The CDMRP enables investigators to submit proposals at every stage of idea and research development through the award mechanisms offered across its different programs.

The CDMRP has offered award mechanisms that support various types of research, which are grouped into four major categories for this report:

- Basic research: Discovery-driven research for the generation of new ideas, knowledge, hypotheses, or preliminary data to support applied and more advanced research. Examples of this research category include "bench-science" and development of animal models.
- Applied research: Research that includes utilizing basic research findings to develop materiel and knowledge products to prevent, diagnose, or treat diseases, conditions, and injuries. Examples of this category include validation using animal models, technology development, and clinical research without an intervention.
- Advanced research: Late-stage applied research, including testing and refinement of materiel and knowledge products in human subject populations. Examples include clinical research with an intervention and clinical trials.
- Combination research: Research utilizing a variety or blend of basic, applied, or advanced research approaches. Award mechanisms and individual awards that span across basic, applied, and advanced research fall into this category. Combination mechanisms are designed to be flexible to allow the research community to propose research at any stage that has the potential for high impact.

Table 1 depicts the award mechanisms offered by the CDMRP since FY1993, classified by the type or stage of research targeted in each. The estimated funding in the investment strategy to support basic, applied, and advanced research is closely matched to the actual award funding investments. Over the lifetime of the CDMRP, the largest percentage of research awards were

made in the combination research category, which utilizes a blend of basic, applied, and/or advanced research. The CDMRP's history of investing in combination research award mechanisms, which allow for maximum flexibility in supporting research in areas where the research landscape is highly dynamic, reflects the responsive approach CDMRP takes to research management. Many of the projects funded through combination research award mechanisms are applied in nature, but even basic research is performed with an eye toward clinical translation. Each application submitted to a CDMRP funding opportunity must provide an Impact or Relevance statement that relates the proposed work to the patient populations that will be affected by the anticipated results. Many award mechanisms also require the submission of a Transition Plan as part of the application package, which describes how the outcomes of the work would move onto the next stage of development and/or clinical application. These features, as well as the inclusion of consumers in peer review and programmatic panels, push each program to focus on the translational potential of each project as an important consideration during funding selection.

Basic research is generally funded using award mechanisms with funding limits in the relatively lower dollar range of $100,000 to $500,000, whereas advanced research involving clinical trials offers more funding, typically in the $1M to $10M per award range. Applied research typically falls between the two in funding requirements, in the $500,000 to $3M range. The high percentage of funding opportunities that seek translational research applications, as well as the corresponding actual awards funded, indicate that supporting translational research is a high priority for the CDMRP.

Table 1. Investment Strategy and Research Funded by Type of Research FY1993 – FY2015*

Type of Research	Award Mechanisms in Investment Strategy	Estimated Funding In Investment Strategy	Percent of Actual Awards	Percent of Actual Award Funding
Basic	24%	11%	34%	10%
Applied	15%	11%	7%	12%
Advanced	13%	10%	3%	9%
Combination	48%	68%	56%	69%

*FY2015 awards are in negotiations and are not final.

For a more detailed analysis of the individual CDMRP research programs, Appendix A shows the planned investment strategy in the left column compared to the actual research awards funded in the right column for each program. The differences in investment strategies among the programs are the result of several factors. The feasibility of offering award mechanisms that support advanced research (which includes clinical trials) may be limited due to gaps in the basic science knowledge of the specific disease or condition, limited availability of funds to support advanced research such as clinical trials, or strategic decisions based on program focus within the broader research landscape. Research programs with less mature areas of research generally focus primarily on basic or applied research in an effort to fill gaps and create the foundations needed for advanced research. Moreover, each CDMRP research program's investment strategy is defined on an annual basis, when the program receives Congressional funding, to identify and

target the areas that are most critically in need of research. Therefore, the award mechanisms and research types supported by a program may shift and evolve over time.

The number of research awards made and funds invested in each type of research vary by program. Each research program's investment strategy is used as a guide when its programmatic panel recommends applications for funding. The actual number of awards recommended for funding and the amount invested within each award mechanism and research type are highly dependent on the number, quality, and type of applications received, as well as each application's relevance to the program's goals, relative innovation or impact, portfolio balance or composition, and adherence to the intent of the award mechanism.

RECENT INVESTMENTS AT A GLANCE: FY2013 – FY2015

To examine more recent CDMRP investments over the last three years, Table 2 depicts the research awards made by the CDMRP during FY2013 – FY2015. The largest percent of all of the CDMRP research awards made (based on number of awards) are in the categories of basic and combination research. Because validation in animal models, clinical research, and clinical trials are generally more costly than basic research, the percentage of research awards made per research type is not directly correlated to the amount of funding invested in each research type. While 28 percent of the CDMRP's FY2013 – FY2015 research awards were in basic research, this represented only 9 percent of the research funding invested. In contrast, while only 7 percent of the FY2013 – FY2015 research awards were specifically in advanced research (clinical trials), this represented 15 percent of the research funding invested. Moreover, in comparison to the data in Table 1, it is evident that the CDMRP's recent research award portfolio is shifting to emphasize more applied and advanced clinical research. For example, applied research represents 12 percent of the award funding within CDMRP's entire portfolio (FY1993 – FY2015), and 22 percent of the award funding in the more recent time period of FY2013 – FY2015. Similarly, the investment in advanced research has grown from 9 percent of the award funding from FY1993 – FY2015, to 15 percent of the award funding in FY2013 – FY2015.

Table 2. Recent Investments by Type of Research, FY2013-FY2015*

Type of Research	Percent of Actual Awards	Percent of Actual Award Funding
Basic	28%	9%
Applied	18%	22%
Advanced	7%	15%
Combination	47%	54%

*FY2015 awards are in negotiations and are not final.

Further evidence of a shift toward more applied and advanced research is seen in comparing the types of research funded over the most recent past three-year intervals. As shown in Table 3, the CDMRP's portfolio reflects a significant shift in the type of research funded when comparing FY2013 – FY2015 to FY2011 – 2013. The greatest increases occurred in applied and advanced research awards, with shifts of 12 percent and 58 percent, respectively, when comparing the

portion of the research portfolio these award types held in each time period. Basic research awards saw a slight decrease of 2 percent, and the portion of awards within the portfolio supported under combination research award mechanisms decreased by 8 percent. This suggests that in addition to increasingly prioritizing funding for applied and advanced research, some programs are relying more heavily on the use of funding opportunities that target a particular phase of research, rather than combination-type funding opportunities that solicit multiple phases of research.

Table 3. Variance Analysis of Research Funded in FY2011 – FY2013 and FY2013 – FY2015*

Type of Research	Percent Change of Actual Awards Funded
Basic	-2%
Applied	+12%
Advanced	+58%
Combination	-8%

*FY2015 awards are in negotiations and are not final.

Appendix B breaks down the recent three-year investments for each of the CDMRP's research programs. Each program has a unique vision that targets the most critical aspects along the pipeline of basic to advanced research. In many cases, the fundamental understanding of the biology and etiology of a disease is still underdeveloped and requires delineation before the gap between basic and advanced research can be bridged. In addition, the research and funding landscape in certain diseases may warrant an emphasis on funding the earlier stages of research, where novel discoveries are critical and urgently needed. A greater emphasis on basic and applied research is evident in programs such as the Peer-Reviewed Amyotrophic Lateral Sclerosis Research Program, the Peer-Reviewed Lung Cancer Research Program, the Peer-Reviewed Ovarian Cancer Research Program, the Peer-Reviewed Prostate Cancer Research Program, the Peer-Reviewed Cancer Research Program, and the Peer-Reviewed Tuberous Sclerosis Complex Research Program. In contrast, other programs such as the Peer-Reviewed Autism Research Program, the Peer-Reviewed Breast Cancer Research Program, the Peer-Reviewed Neurofibromatosis Research Program, the Joint Warfighter Medical Research Program (JWMRP), the Peer-Reviewed Orthopedic Research Program (PRORP), the Orthotics and Prosthetics Outcomes Research Program, the Peer-Reviewed Spinal Cord Injury Research Program, and the Peer-Reviewed Gulf War Illness Research Program, are positioned to solicit for and select research proposals that are closer to clinical translation, through funding

opportunities targeting advanced research and/or the entire translational research continuum (combination research).

TRANSLATING CUTTING-EDGE BASIC RESEARCH INTO CLINICAL PRACTICE

Success in translational medicine demands a continuous pipeline of basic and applied research discoveries that can advance to clinical application.

In an era of numerous biomedical advancements, the increased ability to prevent, detect, and treat diseases, injuries, and medical conditions is providing patients with an array of clinical and preventative interventions and an overall better quality of life. While these advances have been extraordinary in moving medicine forward, many conditions still do not have a cure or cannot be prevented. Thus, the need to accelerate the pace of current biomedical research efforts remains urgent. Advanced research in the form of clinical trials is the engine that drives progress against disease by rigorously testing the safety and efficacy of new products and potential treatments in patients. However, prior to the translation of scientific findings into clinical trials, an increase in the basic understanding of key disease processes must occur and must be substantiated through preclinical investigations in *in vitro* systems and in more complex systems including animal disease models.[4] Therefore, success in translational medicine demands a continuous pipeline of basic and applied research discoveries that can advance to clinical application.

Many of the CDMRP-managed basic and applied projects have the potential to become fielded products for the Service member and civilian populations. One process that helps facilitate this transition is called Decision Gate, a process designed and implemented by the USAMRMC to manage medical product development in a cost-effective, consistent, and transparent manner. Decision Gate, which is grounded in the Department of Defense 5000 series, Food and Drug Administration (FDA) regulations, and best industry practices, allows the USAMRMC to remain responsive to the changing needs of the Service member. Research products identified as having sufficient scientific maturity and potentially filling a documented Service member need enter into Decision Gate. During the continued development of a research product, the product proceeds through a series of decision points (called Milestones) in which the Milestone Decision Authority decides whether product development continues as planned, continues with a revised plan, or is terminated. The CDMRP has participated in the formation of several teams in the Decision Gate process that are working to improve transfusion safety and diagnosis, neurocognitive assessments, diagnosis of traumatic brain injury, and treatment of traumatic brain injury. For CDMRP-supported products that are not specific to current Army capability gaps, further development is often supported by industry, and several examples of this are included in Appendix C.

As another approach to maintain movement of promising basic and applied research along the translational research continuum, some of the CDMRP programs offer Expansion awards. Expansion awards provide support for previous awardees funded through specific award mechanisms to enable the continued investigation of successful innovative ideas and expansion to translational and clinical research. Expansion awards are competitive, undergo the CDMRP's two-tier review, and support further development of research that will impact patient care. In addition, the CDMRP manages the JWMRP, which was initiated by Congress in FY2012 to augment and accelerate high priority research efforts with prior Congressional funding. The

JWMRP allows previous awardees from any Congressionally-funded program to compete for additional funding in support of efforts with high potential impact to military medicine that are ready to transition to late applied or advanced stages of research.

Funding from the CDMRP has enabled several investigators to bridge the gaps between basic science, applied science, and clinical medicine in a broad spectrum of patient-centered areas including treatment, prevention, early detection and screening, diagnosis, and quality of life/supportive care. Appendix C provides an extensive list of CDMRP-funded research efforts that were initiated as basic or applied research, and are currently in or entering a more advanced phase of development such as clinical trials, have been commercialized, or have been implemented as standard of care. Selected examples of CDMRP-funded research that began as basic research and then translated into advanced research or standard of care are highlighted below:

- Amyotrophic Lateral Sclerosis (ALS): Supported an FY2010 award to perform large screens of FDA-approved drugs and identify chemical modifiers of the Tar DNA binding protein of 43 kDa (TDP-43) associated with ALS. The neuroleptic compound pimozide was found to improve neuromuscular transmission and restore mobility in all TDP-43 models tested. These findings led to a Phase IIb clinical trial in Canada to test the effectiveness of pimozide in ALS patients.
- Autism: Supported an FY2010 pilot clinical trial award investigating whether Cognitive Enhancement Therapy or Enriched Supportive Therapy improved outcomes for adults with Autism Spectrum Disorder. After 18 months, the adults in the Cognitive Enhancement Therapy group had significantly higher gains in neurocognition, social cognition, and social adjustment. The results have led to a large follow-on clinical trial funded by the National Institutes of Health (NIH).
- Bone Marrow Failure: Supported an FY2009 study that developed a Myelodysplastic Syndrome (MDS) gene expression repository from MDS bone marrow samples which was subsequently used to determine that transforming growth factor-β (TGF-β) is activated in low risk subtypes of MDS. This study led to an ongoing clinical trial of LY-2157299, an inhibitor targeting the receptor of TGF-β.
- Breast Cancer: Supported an FY2010 study to identify targets and develop a vaccine for primary prevention of breast cancer. A multi-antigen vaccine (STEMVAC) targeting five cancer stem cell proteins was developed and tested in animal models of breast cancer. FDA Investigational New Drug (IND) status was granted and a Phase I clinical trial will conclude in 2016. If STEMVAC proves to be safe, clinical testing will proceed into the primary prevention setting. STEMVAC has been licensed to EpiThany.
- Duchenne Muscular Dystrophy: Supported an FY2012 preclinical study that evaluated the dose response and functional muscle correlation of intramuscular delivery of gene therapy vectors overexpressing the human GALGT2 gene in animal models. The preclinical data supported a successful IND filing with the FDA and led to an NIH-funded Phase I gene transfer clinical trial for Duchenne muscular dystrophy.
- Gulf War Illness (GWI): Supported an FY2008 award to map exercise stress in GWI patients using physiological measures and blood-borne biomarkers. The study predicted

that down-regulation of NF-κB gene expression may bring altered regulatory pathways back to a more normal state. These investigations led to an FY2015-funded Phase I/II evaluation of two nutraceuticals known to down-regulate NF-κB in Veterans with GWI.

- Lung Cancer: Supported an FY2011 project that optimized chimeric antigen receptor (CAR)-T cell immunotherapy against mesothelin-expressing tumor cells in aggressive lung adenocarcinoma. This contributed directly to an ongoing Phase I clinical trial that is investigating the safety, efficacy, and outcomes of CAR-T cell immunotherapy for patients with mesothelioma, lung cancer, or breast cancer.
- Multiple Sclerosis: Supported an FY2009 project that developed an effective myeloperoxidase (MPO) targeted magnetic resonance imaging agent for detection of multiple sclerosis disease activity, setting the stage for clinical investigations into MPO as an early detection strategy for multiple sclerosis.
- Neurofibromatosis (NF): Supported an FY2000 project that resulted in the discovery that Gleevec, a competitive tyrosine-kinase inhibitor already FDA-approved for use in the treatment of multiple forms of cancer, could block the ability of NF1+/- mast cells to stimulate fibroblast proliferation in an animal model, suggesting that it might work to prevent neurofibromas in patients. The results of this study allowed for the fast track approval for a Phase II trial of Gleevec in children and adults with NF1.
- Ovarian Cancer: Supported an FY2003 study in which preliminary investigations identified 5 new biomarkers for ovarian cancer. These biomarkers were validated in more than 3,000 samples and subsequently incorporated into an *in vitro* diagnostic multivariate index test. This blood test, labeled OVA1^{TM}, was approved by the FDA in 2009 and is currently the only approved blood test to help determine if an ovarian mass is malignant or benign prior to surgery. This diagnostic test allows physicians to more easily identify patients for referral to a gynecologic oncologist and aids in facilitating surgical planning for those women who need treatment.
- Parkinson's Disease: Supported an FY2006 award that identified the effects of a calcium ion channel that acts as a pace-maker for activity of the substantia nigra dopaminergic neurons, the loss of which is the proximate cause of Parkinson's disease (PD). These promising results led to a study that identified a candidate compound that has been shown to safely block the calcium ion channel and is in clinical trials to test its efficacy as a disease-modifying treatment for PD.
- Peer Reviewed Alzheimer's: Supported an FY2011 study that revealed that transgenic mice prone to developing Alzheimer's-like pathology did not heal after traumatic brain injury (TBI), and that lesion size grew significantly after TBI. Additional work has since identified a protein implicated in the process, TREM2, which is under investigation in follow-on human studies.
- Peer Reviewed Cancer: Supported an FY2011 research award investigating immune signaling dysregulation in MDS that led to the development of an antibody to Toll-like Receptor 2. The antibody is being manufactured and tested in Phase I/II clinical trials in partnership with Opsona Therapeutics.

- Peer Reviewed Medical: Supported an FY2009 award that demonstrated that combining multiple polyamine-targeting drugs with conventional chemotherapy is more effective in eliminating neuroblastoma in cell lines and animal models. This work led directly to an ongoing Phase I clinical trial using difluoromethylornithine and Celecoxib together with the chemotherapy agents Cyclophosphamide and Topotecan in children with relapsed neuroblastoma.
- Peer Reviewed Orthopaedic: Supported an FY2009 award that enabled development of a prototype prosthetic socket device with vacuum-assisted suspension designed for highly active transfemoral prosthesis users. Subsequent funding from the JWMRP provided for testing of the prototype on four patients with transfemoral amputation. The device, termed the NU-FlexSIV Socket, is now being assessed in a definitive clinical trial supported by the PRORP. Information gathered from the trial will aid providers in prescribing this new socket technology for above-the-knee amputees.
- Prostate Cancer: Supported an FY2002 study, which demonstrated that inhibition of the protein RANKL blocks progression of prostate cancer bone metastases in an animal model. This study led to FDA approval of denosumab as a treatment for cancer-related bone loss and standard of care treatment for osteoporosis (PROLIA®) and cancer (XGEVA®).
- Psychological Health/Traumatic Brain Injury: Supported an FY2007 pilot study to develop and evaluate a brief cognitive-behavioral therapy (CBT) protocol for treating post-traumatic stress disorder (PTSD). The results of this study led to an ongoing randomized, controlled clinical trial of CBT in Service members and Veterans from Operation IRAQI FREEDOM and Operation ENDURING FREEDOM with PTSD symptoms.
- Spinal Cord Injury: Supported an FY2009 study showing that high Schwann cell concentrations are effective in treating spinal cord injury in an animal model. This led to initiation of a Phase I clinical trial of Schwann cell therapy for sub-acute treatment of spinal cord injury.
- Tuberous Sclerosis Complex (TSC): Supported an FY2006 study investigating the role of the mTOR signaling network in TSC. A landmark discovery that mTORC1 signaling regulates TSC led to subsequent clinical trials, resulting in the first drug approved by the FDA specifically for the treatment of TSC.

The above-mentioned research represents only a few examples of the clinical products or approaches that have arisen from basic and applied research supported by the CDMRP that have made, or have the potential to make, a significant clinical impact.

MAKING AN IMPACT THROUGH CLINICAL TRIALS

Another aspect of the CDMRP's research portfolio that demonstrates commitment to making a clinical impact is the significant funding invested in clinical trials. Currently, 338 active (open or pending) awards across the programs managed by the CDMRP include clinical trials. Some of these awards support more than one clinical trial, such as the clinical consortia awards offered by several programs. The types of clinical trials include, among others, innovative detection

methods, novel cognitive treatments, vaccines and immunotherapies, physical therapies, and therapeutic drug interventions. As shown in Figure 1, more than a quarter of the active awards with clinical trials are being supported by the Psychological Health/Traumatic Brain Injury Research Program (PH/TBIRP), while the other awards with clinical trials are distributed across twenty different programs.

Advanced research supporting clinical trials constitutes a significant portion of the CDMRP's research and funding investments.

For programs with currently active clinical trials, the bar graphs in Figure 2 depict program-specific data on the percentage of awards and dollars invested in awards with clinical trials within each program's active research award portfolio. For ease of display, the programs have been divided between two graphs that depict the same type of information. The dollars invested in awards with clinical trials represent as much as 56 percent and 55 percent of the current research portfolios of these CDMRP programs
(the PH/TBIRP and the PRORP, respectively). While the number of active awards with clinical trials represents 11 percent of the total number of awards across all of these programs combined, notably the percent of funding invested in awards with clinical trials represents 28 percent of the total active investments. Taken together, these data demonstrate that advanced research supporting clinical trials constitutes a significant portion of the CDMRP's research and funding investments.

Figure 1. Distribution of CDMRP's Active Awards with Clinical Trials by Research Program

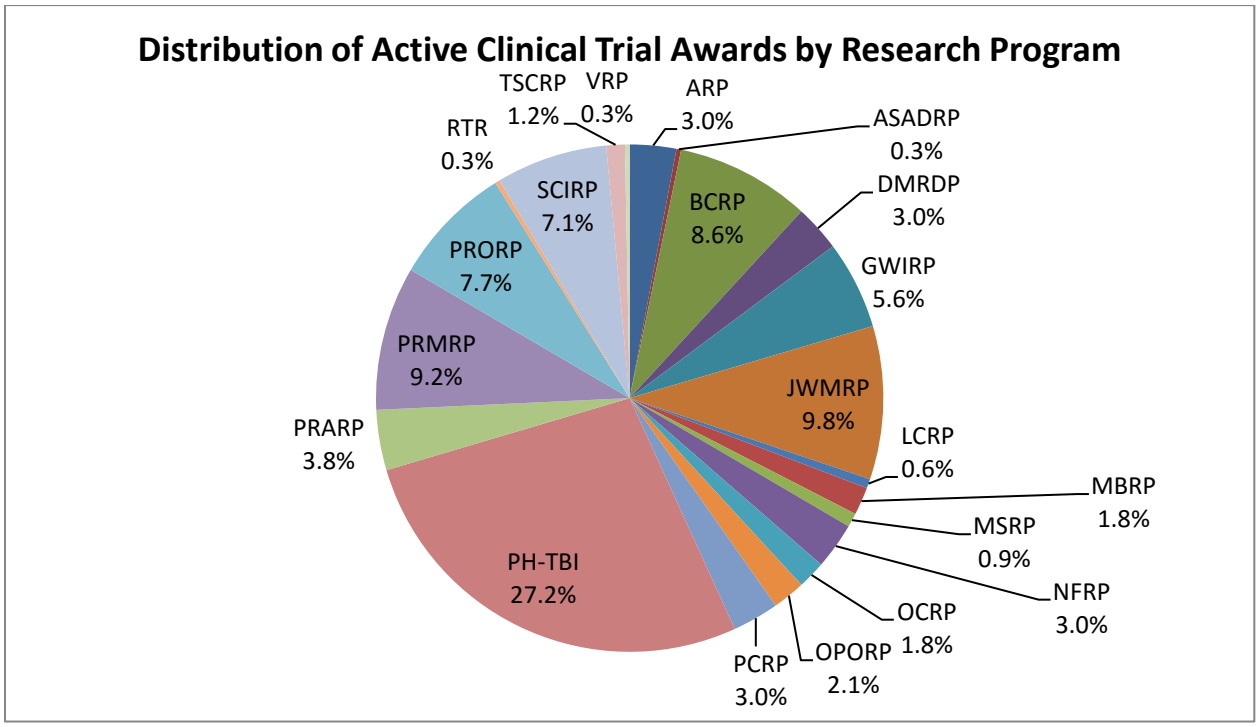


Figure 2. Distribution of Awards with Clinical Trials by Research Program

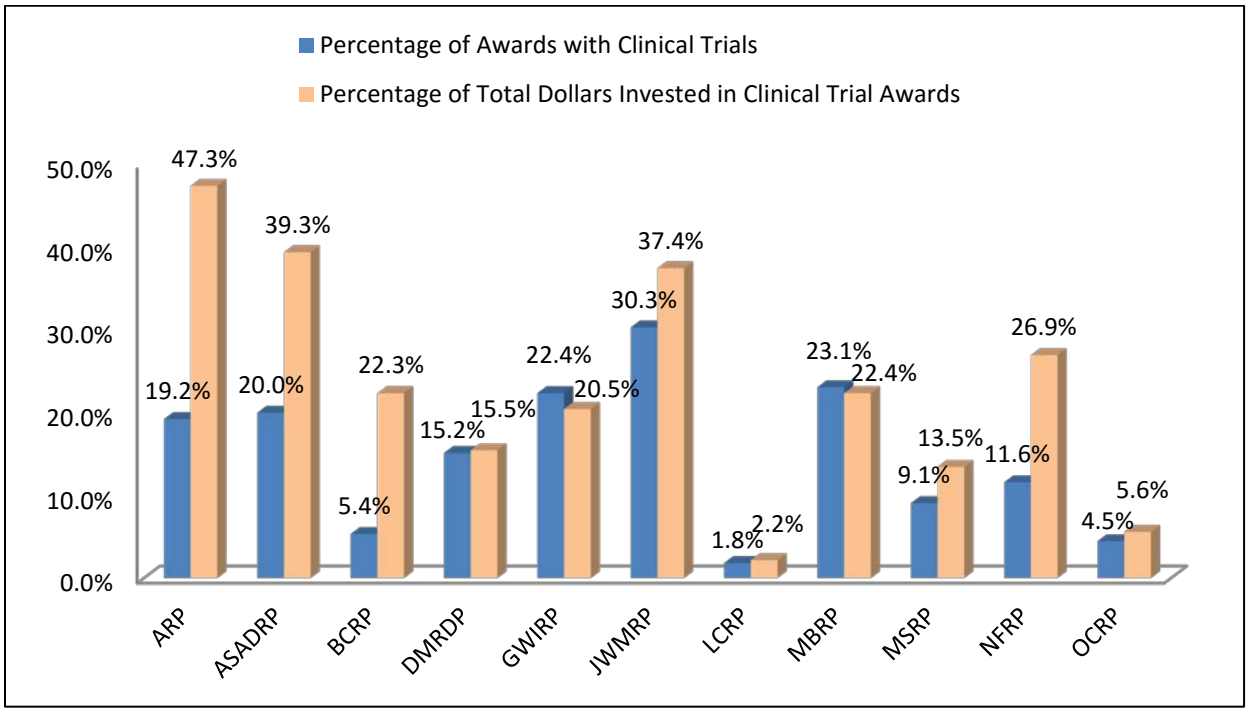
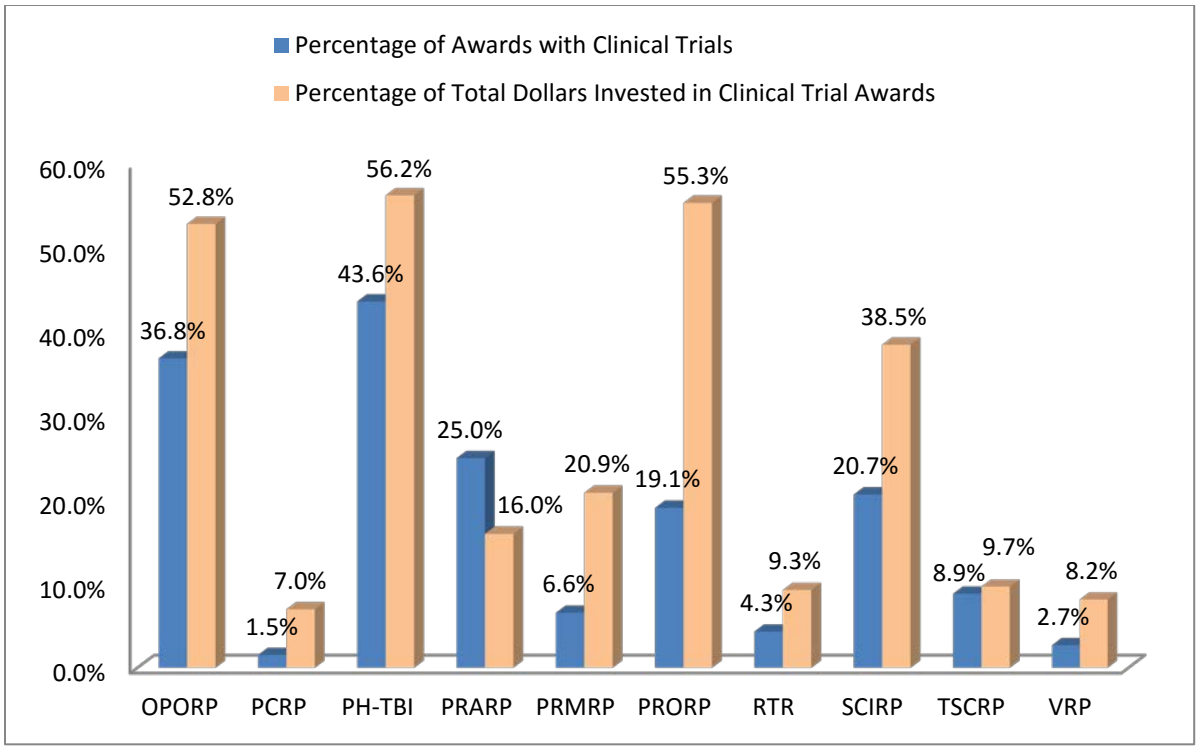


Figure 2. Distribution of Awards with Clinical Trials by Research Program (cont'd)



SUMMARY

Research programs managed by the CDMRP establish annual investment strategies that target the type of research that not only will meet each program's vision and goals, but fill gaps in the research field and funding landscape. The CDMRP's programs are able to shift the focus of their award mechanisms as needed to target the most critical needs along the pipeline of translating basic research to the clinic**.** Its partnership with consumers is a critical component of establishing research opportunities and funding awards that are best poised to discover, develop, and deliver innovative health care solutions for Service members and the civilian population alike. Translational research is a high priority of the CDMRP, as evidenced by the frequent use of funding mechanisms which seek translational research projects in applied and combination research, as well as the significant funding subsequently invested in these translational research categories. Moreover, more than one-quarter of the CDMRP's awards include a clinical trial, so it is clear that supporting advanced research is a priority of the CDMRP. Importantly, many investments made in basic or applied research projects have successfully achieved advanced development and are now clinical standards of care, resources, or products benefiting patients or the research field. By enabling funding of high-gain research efforts in all phases of the research pipeline, and supporting investigators that possess the passion and creativity to pursue transformative research, the outcomes of CDMRP-funded research have a high probability to continue making translational research advancements and clinical breakthroughs.

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LIST OF PROGRAM ACRONYMS

Program	Acronym
Alcohol and Substance Abuse Disorders Research Program	ASADRP
Amyotrophic Lateral Sclerosis Research Program	ALSRP
Autism Research Program	ARP
Bone Marrow Failure Research Program	BMFRP
Breast Cancer Research Program	BCRP
Defense Medical Research and Development Program	DMRDP
Duchenne Muscular Dystrophy Research Program	DMDRP
Epilepsy Research Program	ERP
Gulf War Illness Research Program	GWIRP
Joint Warfighter Medical Research Program	JWMRP
Lung Cancer Research Program	LCRP
Military Burn Research Program	MBRP
Multiple Sclerosis Research Program	MSRP
Neurofibromatosis Research Program	NFRP
Orthotics and Prosthetics Outcomes Research Program	OPORP
Ovarian Cancer Research Program	OCRP
Parkinson's Research Program	PRP
Peer Reviewed Alzheimer's Research Program	PRARP
Peer Reviewed Cancer Research Program	PRCRP
Peer Reviewed Medical Research Program	PRMRP
Peer Reviewed Orthopedic Research Program	PRORP
Prostate Cancer Research Program	PCRP
Psychological Health/Traumatic Injury Research Program	PH/TBIRP
Reconstructive Transplant Research Program	RTRP
Spinal Cord Injury Research Program	SCIRP
Tuberous Sclerosis Complex Research Program	TSCRP
Vision Research Program	VRP