Multiple Sclerosis Research Program

Congressionally Directed Medical Research Programs

CDMRP

Department of Defense

U.S. Army Medical Research and Development Command

Congressionally Directed Medical Research Programs

HISTORY: The Office of the Congressionally Directed Medical Research Programs (CDMRP) was established in 1992 from a powerful grassroots effort led by the breast cancer advocacy community that resulted in a congressional appropriation of funds for breast cancer research. This initiated a unique partnership among the public, Congress, and the military. Since then, the CDMRP has grown to encompass multiple targeted programs and has received over $15 billion in appropriations from its inception through fiscal year 2020 (FY20). Funds for the CDMRP are added to the Department of Defense (DOD) budget, in which support for individual programs such as the Multiple Sclerosis Research Program (MSRP) is allocated via specific guidance from Congress.

APPLICATION REVIEW PROCESS: The CDMRP uses a two-tier review process for proposal evaluation, which is critical to ensuring that each of the research program portfolios reflects not only the most meritorious science, but also the research that best meets the program goals. The first tier of evaluation is a scientific peer review of applications, measured against established criteria determining their scientific merit. The second tier is a programmatic review, conducted by a Programmatic Panel composed of leading scientists, clinicians, and multiple sclerosis (MS) consumers. In this tier, the Programmatic Panel compares applications to each other and makes recommendations for funding based on scientific merit as determined in peer review, potential impact, portfolio balance, and relevance to overall program goals.

Multiple Sclerosis Research Program
ABOUT MS AND THE PROGRAM

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

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

MS is a chronic immune-mediated disease that causes damage to the central nervous system (CNS) (brain and spinal cord) and affects nearly 1 million individuals in the United States.[1] MS is characterized by the demyelination of axons due to the immune system incorrectly attacking healthy tissues in the CNS. While MS can affect individuals of all ages, it is more commonly diagnosed in young adults, particularly women, between the ages of 20 and 50. While research indicates that early exposure to certain environmental factors in genetically susceptible individuals may trigger the disease, the etiology and pathogenesis of MS are largely unknown. Symptoms of MS vary widely in type and severity and may include pain, fatigue, depression, anxiety, loss of bladder control, impaired mobility, and cognitive, motor, visual, or sexual dysfunction. Currently, there is no cure for MS. Congress first appropriated funds establishing the MSRP in FY09. Since then, a total of $93.1 million (M) has been appropriated to the program, including an increase in funds totaling $20M in FY21.

Military Relevance

MS has a higher incidence in US Armed Forces personnel than in the general population[2]. Between 2009 and 2018, more than 2,400 active duty and reserve and National Guard Service members received a new diagnosis of MS within the MHS. Including other DOD beneficiaries such as former Service members and family members, the MHS had more than 21,000 new cases of MS. During this period, more than 36,000 DOD beneficiaries had over 1.1 million outpatient encounters and 537,000 hospital bed days for MS within the MHS[3]. In addition, the Department of Veterans Affairs Multiple Sclerosis Centers of Excellence, East and West branches, serve approximately 49,000 Veterans with MS[4].

[1] Wallin MT, *et al.* The prevalence of MS in the United States: A population-based estimate using health claims data. *Neurology*. 2019 Mar 5;92(10):e1029-e1040.

[2] Eussing EC, *et al.* Estimated incidence of multiple sclerosis among United States Armed Forces personnel using the Defense Medical Surveillance System. *Mil Med*. 2012 May;177(5):594-600.

[3] Data includes both direct care (care received at Military Treatment Facilities) and purchased care (care received at Civilian facilities that is covered by TRICARE). Data does not include care received while deployed, or any care received outside of the Military Health System that was not processed through TRICARE.

[4] Gromisch ES, *et al.* Who is not coming to clinic? A predictive model of excessive missed appointments in persons with multiple sclerosis. *Mult Scler Relat Disord*. 2020 Feb;38:101513.
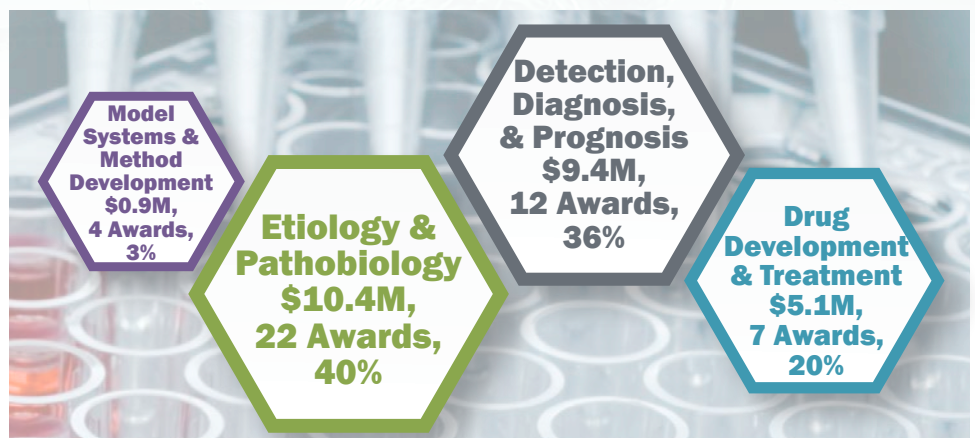
Strategic Plan

In 2018, the MSRP developed a Strategic Plan that specifies the strategic goals and investment direction of the program. It recognizes that a broad range of unanswered research questions are potentially critical to advancing prevention, diagnosis, and treatment of the diverse symptoms of MS with the ultimate goal to find a cure. The current Overarching Strategic Goals are shown in the following graphic. In order to achieve these Strategic Goals, the MSRP identified a corresponding scientific priority area or focus area under each of these goals. These focus areas are integrated into the program announcements and guide the investment of the program. Since the fourth focus area was introduced in FY20, no investment under this focus area is shown from FY15 through FY19.

Strategic Goals	Focus Areas	Investment
Understand, measure, and treat relapsing and progressive aspects of MS	Correlates of disease activity and progression in MS	$10.7M 15 Awards
Identify strategies for neuroprotection, repair and restoration of function, and ultimately improving symptoms and quality of life	Central nervous system regenerative potential in demyelinating conditions	$6.8M 11 awards
Elucidate the cause and pathophysiology of MS symptoms that have a high impact on quality of life and develop treatment strategies	Biology and measurements of MS symptom	$8.2M 19 awards
Identify the factors that contribute to MS etiology and disease course	Factors contributing to MS etiology, prodrome, onset and evolution (*New in FY20*)	N/A

RESEARCH SPECTRUM

Guided by its vision and mission, the MSRP has funded research projects focused on understanding the underlying signaling pathways and disease etiology; developing disease models to further understand the disease; improving detection, diagnosis, prognosis; and developing new therapeutic approaches. Analysis of the most recently funded research projects (FY15–FY19) is reflected in the graph below, indicating the percentage of the program's research investment in each area.
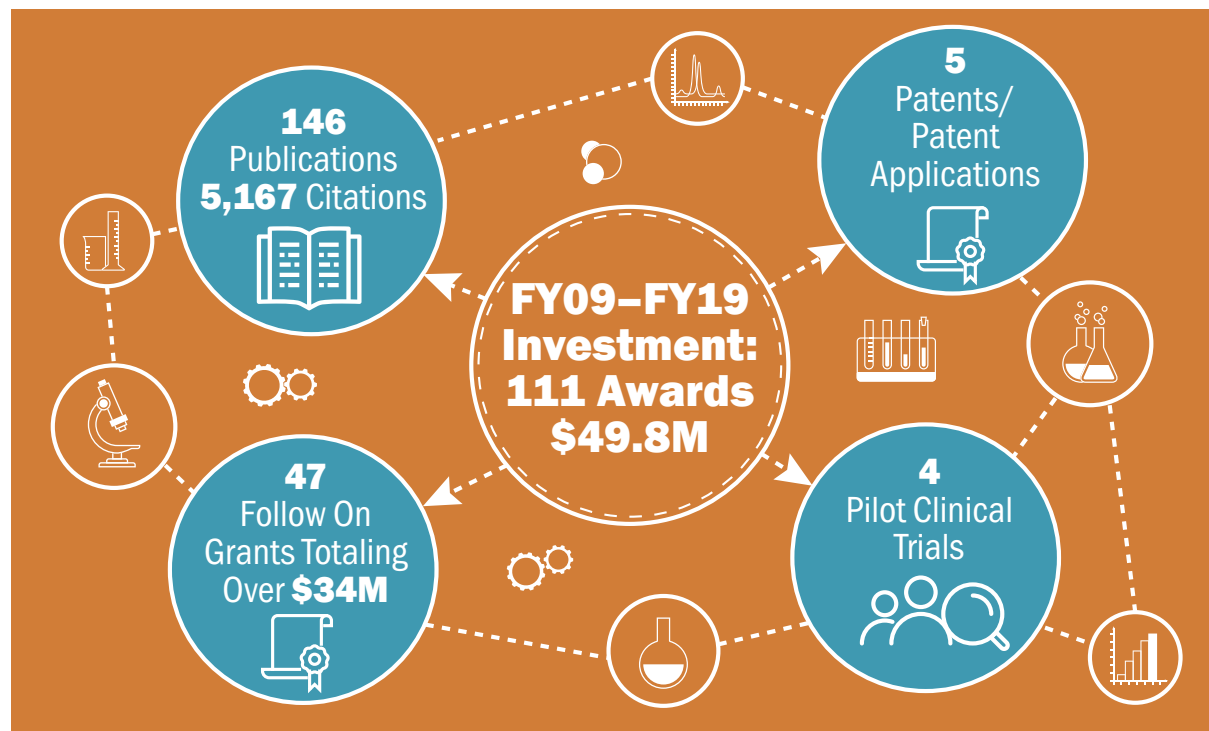
While research in many of these basic science categories does not always immediately produce new treatments, these investigations are critically important because they can reveal molecular targets or pathways that can lead to new treatments. Furthermore, previous MSRP-funded studies to develop models and understand the biology and etiology of MS have led to significant advances in the field.

Model Systems & Method Development $0.9M, 4 Awards, 3%

Etiology & Pathobiology $10.4M, 22 Awards, 40%

Detection, Diagnosis, & Prognosis $9.4M, 12 Awards, 36%

Drug Development & Treatment $5.1M, 7 Awards, 20%

The numbers in each cell represent the total funding in millions, the number of awards, and the percentage of investment in dollars.

Research Outcomes

MSRP-funded research projects have resulted in numerous impactful outcomes, including high-impact publications, knowledge- and data-sharing at scientific and patient-focused conferences, follow-up research grants from other federal and non-federal funding agencies to further expand their MSRP-funded studies, and patents/patent applications. The MSRP-funded pilot clinical trials aim to improve cognition, reduce fatigue, or increase mobility in people with MS, to enhance their quality of life.

Pilot Clinical Trials	
Ellen Mowry, M.D., Johns Hopkins University	NCT02988401: Evaluate whether insulin is safe and tolerable in people with MS and can improve their cognition. Enrollment is complete. Data analysis is underway.
Kottil Rammohan M.D., University of Miami	NCT03266965: Study is complete and shows L-histidine reduces fatigue in patients with MS. Follow on studies are planned to replicate the trial with larger enrollment numbers.
Joel Stein, M.D, Columbia University Medical Center	NCT03230903: Assess the feasibility and impact of an innovative home-based physical telerehabilitation model in MS patients with significant mobility impairment. Enrollment is complete and data analysis is underway.
Leigh Charvet, Ph.D., New York University School of Medicine	NCT03499314: Evaluate the efficacy of a remotely supervised platform to enhance hand rehabilitation in individuals living with progressive MS with reduced manual dexterity. Ongoing.

Patent/Patent Applications	
Award Number	Patent Citation (Inventor Name (Year), Title of Patent/Patent Application, Patent/Patent Application Number)
MS090152	Field (2013) Method for determining and ordering K-space views and diffusion weighting directions. US Patent No. 8482284
MS100248	Zabel (2015) Small molecule CMKLR1 antagonists in demyelinating disease. US Patent No. 9265738
MS100248	Zabel (2017) Methods of enhancing anti-tumor immunity by administering antibodies to the ccrl2 chemerin receptor. US Patent No. 9868792
MS110080	Moore (2017) Neural microphysiological systems and methods of using the same. US Patent Application Publication No. US 2017-0276668 A1
MS110215	Letterio (2020) Tolerogenic dendritic cells and uses thereof. WO 2020/215013 A1.

Scientists and Consumers Working Together

The two-tier review process established by the CDMRP brings together the expertise of scientists with the perspective and experience of individuals living with MS (consumers). This innovative approach has proven to be an effective way to evaluate research applications for their potential to meet the program's goals for those impacted by MS. Consumers have an equal voice in setting the MSRP's vison, reviewing applications, and making final funding recommendations. From their unique perspective gained through personal experience, consumers bring a sense of urgency and focus to each part of the program cycle. Consumers evaluate the impact of the research to individuals with MS, as well as the needs of their family members and caregivers and the clinicians who treat them. Working together, MS researchers, clinicians, and consumers ensure that the MSRP funds the most relevant, innovative, and high-risk/high-reward projects to end MS.

"I am honored to have served as a Programmatic Panel member the past 3 years. It has been a privilege to have been able to discuss where major directions in MS research need to go, what the crucial unmet needs are, and then to formulate a call for proposals for these critical areas. I am delighted that the United States Congress has seen it fit to continue to fund MSRP, and I look forward to the many exciting discoveries that are made possible from the directions that I have helped guide at MSRP."

V. Wee Yong, Ph.D., Programmatic Panel Member

"Being part of the MSRP program has been extremely rewarding both on a scientific and a personal level. At the programmatic level, I believe that the MSRP fills a critical gap to promote scientific innovation and risky ideas, while promoting cross-pollination among disciplines and between clinicians and bench scientists. On a more personal note, it has been wonderful to work together with MS patients, hear their concerns, and share the same goal to find a cure for MS."

Patrizia Casaccia, M.D., Ph.D., Programmatic Panel Member

"While I had been involved in advocating for the MSRP, it wasn't until I served as a consumer reviewer that I really began to understand what it was all about. In the beginning, as I was reviewing along with these eminent physicians and scientists, listening to them discuss the nuances of the proposals; it was daunting. However, I quickly began to understand that it was not about my ability to distill the scientific underpinnings of the proposals as much as being able to communicate what impact those proposals would have on someone living with MS—to be able to envision what a proposed treatment – or even cure – would mean for those of us living with MS. This is the perspective that we, the consumer reviewers, add to a process that reviews the science and also takes into account the value those potential successes would have for those of us who would be directly impacted by the results."

Greg Schuckman, MSRP Consumer Peer Reviewer

"Reviewing for the MSRP has been very rewarding. Great care is taken for a fair and judicious process for peer review that includes the perspectives of individuals living with MS. I have enjoyed meeting new colleagues and having exposure to exciting, innovative proposals across the spectrum of MS research."

Jennifer Graves, M.D., Ph.D., Scientific Peer Reviewer

Using Reprogrammed Stem Cells as a Therapy for MS

Stefano Pluchino, M.D., Ph.D., University of Cambridge, United Kingdom
Frank Edenhofer, Ph.D., Julius-Maximilian University of Würzburg, Germany
Regina Armstrong, Ph.D., Uniformed Services University of the Health Sciences

REMYELINATION

Dr. Stefano Pluchino   Dr. Frank Edenhofer   Dr. Regina Armstrong

In MS, the disease process is driven by both persistent inflammation and an inability of cells within the CNS to replace damaged myelin (remyelination). Recent advances in stem cell-based therapies led Dr. Pluchino to explore the use of induced neural stem cells (iNSCs) as a potential approach to treating MS. NSCs are "master cells" that can develop into new neurons and myelin-forming cells called oligodendrocytes. Dr. Pluchino previously harvested and transplanted adult NSCs into animal models of MS (experimental autoimmune encephalomyelitis (EAE) mice), which reduced functional impairments and promoted remyelination and recovery of demyelinated neurons. With support from an FY14 Investigator-Initiated Partnership Award, Dr. Pluchino, along with Drs. Edenhofer and Armstrong, aimed to identify the ideal source of stem cells for transplantation and to further define the mechanisms of action in the context of MS pathophysiology. First, the team established methods to induce both mouse and human skin fibroblasts to become NSCs. When these induced iNSC were transplanted in the brains of EAE mice through cerebrospinal fluid (CSF), they produced the same benefits as the iNSCs. There was a significant reduction in clinical deficits, as well as spinal cord demyelination and axon loss. Additional work showed that iNSC transplantation improved coordination, with some improvements also evident in brain imaging of these mice. Interestingly, these recovery effects occurred alongside reduction of succinate in the CSF of the iNSC-transplanted mice. Succinate has been linked to metabolic distress and inflammatory activity in MS, and further investigation revealed that transplanted iNSCs can sense the excess of succinate in the inflamed CNS and reduce its levels by initiating an anti-inflammatory effect. In turn, this causes iNSCs to release the anti-inflammatory prostaglandin, E2. Therefore succinate may serve as a biomarker of brain inflammation, and its reduced levels in the CSF may be associated with improvement of MS-associated clinical deficits and neuropathological features. Currently human iNSCs are being tested in laboratory animals with MS-like lesions, but have not yet been tested in humans. These findings hold promise for translating state-of-the-art cell reprogramming technologies into next-generation, patient-specific, human iNSC therapeutics for progressive MS and other degenerative neurological diseases.

Mitochondrial Dysfunction and Disease Progression in MS

Patrizia Casaccia, M.D., Ph.D., Icahn School of Medicine at Mount Sinai and
Advanced Science Research Center (ASRC) at The Graduate Center of
The City University of New York
Ilana Katz Sand, M.D., Icahn School of Medicine at Mount Sinai
Catarina Quinzii, M.D., Columbia University, Medical Center

SYMPTOMS

Dr. Patrizia Casaccia   Dr. Ilana Katz Sand   Dr. Catarina Quinzii

MS is a disorder of the central nervous system, characterized by inflammatory demyelination and various degrees of neurodegeneration. Clinically, MS is categorized into three phenotypes according to the disease course: relapsing remitting (RRMS), secondary progressive (SPMS), and primary progressive (PPMS). Approximately 85% of people with MS are initially diagnosed with a relapsing-remitting course; however, with aging, approximately half of these patients transition into a progressively debilitating disease course identified as SPMS. The remaining 15% of MS patients are classified as PPMS, presenting with progressive neurological deterioration at disease onset. While therapeutic options are limited, it has been proposed that mitochondrial dysfunction underlies neuronal damage, but the precise molecular and cellular mechanisms remain unclear. With support from an FY14 Investigator-Initiated Partnership Award, Dr. Casaccia, along with her colleagues Dr. Katz Sand and Dr. Quinzii, studied the potential differences

in factors present in the CSF of patients with a relapsing-remitting or progressive disease course. They used cultured rodent neurons exposed to the different CSF samples and performed a morphological and functional screening of mitochondria. They observed that exposure to the CSF samples from progressive but not RRMS patients induced elongated tubular mitochondrial structures that were reminiscent of neurons exposed to conditions of decreased nutrient availability. Further investigation of the composition of the CSF in the two groups of patients, using metabolomic and lipidomic approaches, provided an explanation. The detection of neurotoxic lipids such as C24 cerimide in progressive patients led to a new model of neurotoxicity. Exposure to neurons to this specific ceramide directly impaired their mitochondrial function and also induced a transcriptional response. The increased expression of glucose transporters in ceramide-treated neurons resulted in higher glucose uptake, thereby creating a state of "virtual hypoglycosis," further exacerbating the energetic deficit and neurotoxicity. Taken together, these data suggest that exposure of neurons to factors present in the CSF of MS patients with a progressive disease course leads to a maladaptive mitochondrial response, suggesting differences in the composition of the CSF as the potential basis for neurodegeneration in progressive MS. Currently, the team is deriving neurons from induced pluripotent stem cells from MS patients and plans to characterize their mitochondrial function to further advance the current knowledge and lay the groundwork for identification of potential therapeutic targets.

Role of the Gut Microbiome in Relapsing and Progressive MS

Dr. Sergio Baranzini, Ph.D., University of California, San Francisco
Dr. Bruce Cree, Ph.D., University of California, San Francisco
Dr. Robin Knight, Ph.D., University of Colorado at Boulder

CORRELATES

Dr. Sergio Baranzini   Dr. Bruce Cree   Dr. Robin Knight

Despite all advances in MS genetics, common variation can only explain at most 40% of the phenotypic variance, suggesting the presence of other factors such as epigenetics, gene interactions, environmental variables, or a combination. These factors, as well as age and microbial infections, have all been implicated in the development of autoimmune diseases. Recent studies suggest dysbiosis, or alterations in the gut microbiota, can influence the onset and progression of autoimmune diseases, including MS. In fact, changes in gut microbiota can alter the balance between inflammatory and regulatory host responses and modulate the phenotype, proliferation, and functional capacity of inflammatory/regulatory cells. With support from an FY14 Investigator-Initiated Partnership Award, Drs. Baranzini, Cree, and Knight have studied gut microbiota from two clinically distinct forms of MS and healthy controls. First they aimed to determine whether specific human gastrointestinal microbiota alters the balance of inflammatory and regulatory immune cell populations, leading to disease in genetically susceptible hosts. To study this, they analyzed the microbiota compositions of subjects with RRMS, and PPMS and compared them to healthy controls using ribosomal RNA gene sequencing. They found a significant difference of biodiversity among healthy control, RRMS and PPMS patients, even though the samples were not clearly clustered by disease status. Additionally, they found that three confounders (recruitment site, sex, and body mass index) were significantly associated with microbiome diversity. One microbe belonging to the Enterobacteriaceae family was different between RRMS and controls, while the abundance of Ruminococcus torques, Bacteroides caccae, and Eubacterium dolichum were increased in PPMS patients compared to healthy controls. E. dolichum is associated with propionate production, while R. torques and B. cacca are mucin degradation bacteria. Specifically, R. torques has been shown to be enriched in patients with autism spectrum disorder and inflammatory bowel disease. This team further studied this topic by utilizing experimental models to develop a double transgenic (C57Bl/6) mouse model of MS (experimental autoimmune encephalitis [EAE]) in a germ-free environment. They recolonized the gut of these mice with microflora from a select group of patients with either RRMS or PPMS. They found that EAE scores in mice receiving microbiota from the PPMS subject were significantly lower than in mice receiving microbiota from an RRMS subject. Colonization with microbiota from a control individual resulted in EAE scores that were intermediate between the previous two groups. These data indicate there are some differences in the microbiota in MS patients that impacted EAE scores, pointing to a connection of the microbiota and MS outcomes. In the future, they will continue working with the mouse models to further understand the changes in the microbiota in MS patients. Outcomes of this work will contribute to developing biomarkers of disease progression, therapeutic response, and novel therapeutic approaches based on rational and personalized probiotics.

Above: Emily Reily, Lisa Emrich, and Gary Pinder.
On Cover: Yvette Brisco, John Platt, Nancita Rogers, Tina Rosenthal, and Eduardo Tinoco

For more information, visit
https://cdmrp.army.mil
or contact us at:
usarmy.detrick.medcom-cdmrp.mbx.cdmrp-public-affairs@mail.mil
(301) 619-7071