

# CDMRP



Department of Defense

# Multiple Sclerosis Research Program



U.S. Army Medical Research and Materiel Command



# Congressionally Directed Medical Research Programs (CDMRP)

## HISTORY

The 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 \$12.6 billion in appropriations from its inception through fiscal year 2018 (FY18).

## APPLICATION REVIEW PROCESS

The CDMRP uses a two-tier review process for proposal evaluation, with both tiers involving dynamic interaction among scientists and consumers. The first tier of evaluation is a scientific peer review of proposals, measuring them against established criteria for determining their scientific merit. The second tier is a programmatic review, conducted by a Programmatic Panel composed of leading scientists, clinicians, and consumers. The Programmatic Panel compares proposals to each other and makes recommendations for funding based on scientific merit, portfolio balance, and relevance to overall program goals.



# Multiple Sclerosis Research Program

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

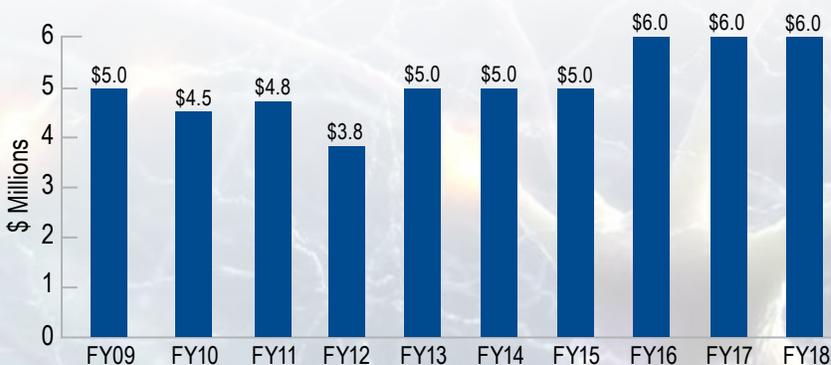
**Mission:** To support pioneering concepts and high impact research relevant to the prevention, etiology, pathogenesis, assessment and treatment of multiple sclerosis for the benefit of Service members, Veterans, and the American public

## ABOUT MS AND THE PROGRAM

Multiple sclerosis (MS) is a chronic, unpredictable disease of the central nervous system (CNS). It is thought to be an immune-mediated disorder where the immune system incorrectly attacks healthy tissues in the CNS. The etiology and pathogenesis of MS are largely unknown, but possibly caused by early exposure to certain environmental triggers in genetically susceptible individuals. MS affects more than 2.3 million (M) individuals worldwide. However, the current prevalence in the U.S. population is difficult to estimate due to many factors, including the lack of a requirement for U.S. physicians to report new cases, complication in diagnosis due to imperceptible symptoms, and lack of a national registry. 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. It occurs in most ethnic groups, but is most common in Caucasians of northern European ancestry. Currently, there is no cure for MS.

Congress first appropriated funds establishing the Multiple Sclerosis Research Program (MSRP) in FY09. Since then, a total of \$51.1M has been appropriated to the program, including \$6M in FY18.

## FY09–FY18 Congressional Appropriations



**On the Cover:** Despite a diagnosis of MS at age 17, Emily Reilly advanced to become an All-American college athlete. She currently instructs adaptive fitness classes for individuals with MS in Northern Virginia. Emily is an active advocate for MS research and care and serves on the MSRP's Programmatic Panel.

# Strategic Plan

In 2018, the MSRP developed a Strategic Plan that specifies the mission of the program, coordination of activities with other organizations, goals and how those goals will be addressed by future award mechanisms, how research outcomes will be tracked, and how outcomes will inform future research initiatives. Details of the Strategic Plan can be found at:

<http://cdmrp.army.mil/msrp/pdfs/MSRP%20Strategic%20Plan.pdf>

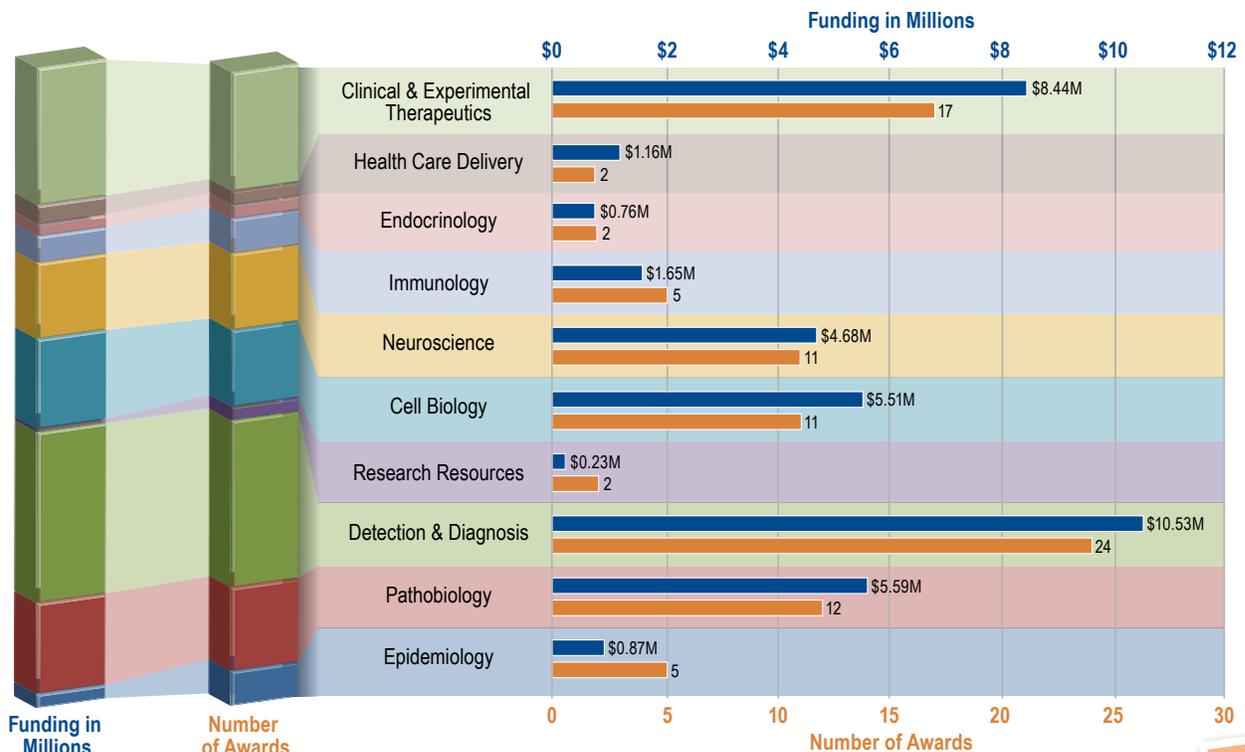
Taking in consideration the funding provided by other federal and non-federal organizations, the state of MS research, and the needs of the scientific and consumer communities, the MSRP will continue its efforts to prevent, cure, reverse, or slow the progression and lessen the personal and societal impact of MS, with the ultimate goal to benefit Service members, Veterans, and the general public.

## STRATEGIC GOALS

- Understand, measure, and treat relapsing and progressive aspects of MS; disease measurement will include clinical outcomes, patient-reported outcomes, and imaging and non-imaging biomarkers.
- Identify strategies for neuroprotection, repair and restoration of function, and ultimately improving symptoms and quality of life.
- Elucidate the cause and pathophysiology of MS symptoms that have a high impact on quality of life and develop treatment strategies.
- Identify the role of various risk factors in MS etiology and disease course.

## MSRP Portfolio FY09–FY17

Of the \$45.1M Congressional appropriation, \$39.5M was used to fund 91 research awards. The portfolio is displayed as the number of awards and amount of funding (in millions) for each research category.



# Scientists and Consumers Working Together



## **Pedaling to New Heights and Improving Lives with MS**

### **Lisa Emrich, Accelerated Cure Project for MS, Consumer Peer Reviewer**

Professional musician Lisa Emrich awoke on the day of a performance with no sight in one eye and was ultimately diagnosed with MS. While the disease has affected her ability to perform, it has also brought new passions to her life, including writing and patient advocacy for MS and cycling for fun and rehabilitation.

Lisa and her husband put a team together for “Bike MS,” an event sponsored by the National MS Society (NMSS). She says one of her greatest cycling challenges is the risk of falling if she rides too slowly.

In that same vein, Lisa says, “Staying in motion helps me to move forward in life,” a philosophy that is evident in her advocacy for those suffering from MS. She authors a healthcare blog, contributes to and monitors health websites, and serves on the Virginia Government Relations Committee for the NMSS. Lisa worked on the launch of iConquerMS.org™ and serves as a patient stakeholder and research proposal reviewer for the Patient Centered Outcomes Research Institute.

Lisa recently served as a consumer reviewer for the MSRP peer review and says, “I am thrilled to contribute to the peer review process and to represent the patient community at large. The passion and commitment displayed during panel meetings was palpable, and the respect with which my opinions were received was greatly appreciated. I highly encourage members of the MS community to get involved, whether through research projects such as iConquerMS.org, raising funds for an advocacy organization, supporting each other in our social networks, or participating in the scientific review process through programs such as the MSRP. We each have something to contribute to ultimately improve the lives of those living with and impacted by MS.”

## **A Multiple Sclerosis Insider**

### **Stephanie Buxhoeveden, M.S.N., FNP-BC, M.S.C.N., MS HOPE Foundation, Consumer Peer Reviewer**

Stephanie Buxhoeveden was on a path for advanced specialized certification as a Nurse Anesthetist when she was diagnosed with MS. Embracing a “make lemonade” philosophy, she changed her career goal from Nurse Anesthetist to Neurology Nurse Practitioner. She flourished in that specialty, rising to the position of co-director of an MS Comprehensive Care Center in Fredericksburg, VA. She has since left clinical practice and acts as a Clinical Science Liaison with Biogen while studying MS biomarkers for her Ph.D. in nursing. She maintains that her MS diagnosis has ultimately led to more positive experiences than negative ones.

Stephanie applies her professional talents to MS advocacy efforts too. She believes that people with MS who become involved in research and advocacy are paving the way to more impactful solutions for the disease. She writes for the MS Hope Foundation, acts as a nursing consultant and outreach participant for Can Do MS, and consults for the MS team on WebMD. She is a District Activist Leader in the National MS Society and serves on her region’s Healthcare Advisory and Government Relations Committees. Stephanie contributes monthly articles to MultipleSclerosis.net, sharing her experiences and educational information about MS.

As a consumer reviewer for the MSRP peer review, she reports that consumer reviewers’ opinions add value, are taken seriously, and are critical to the process. She says, “I am so inspired by how many intelligent, passionate people are working to find solutions. I feel confident that, because of them, we are closer than ever to figuring out what causes MS, finding better treatments, and even finding a cure.”



“It was a wonderful experience to be a part of the MSRP peer review panel. I found it both informative and rewarding to work with scientists, clinicians, and MS advocates to identify promising research for the prevention and treatment of MS.”

### **Jeffrey Huang, Ph.D., Georgetown University, Scientific Peer Reviewer**

“It is very rewarding to participate in the MSRP and help direct these critical investments in MS research to achieve maximum impact. This program provides critical funding that complements and leverages funding by the NMSS and the National Institutes of Health. Together, we will find breakthroughs that will lead to better treatments and a cure for MS.”

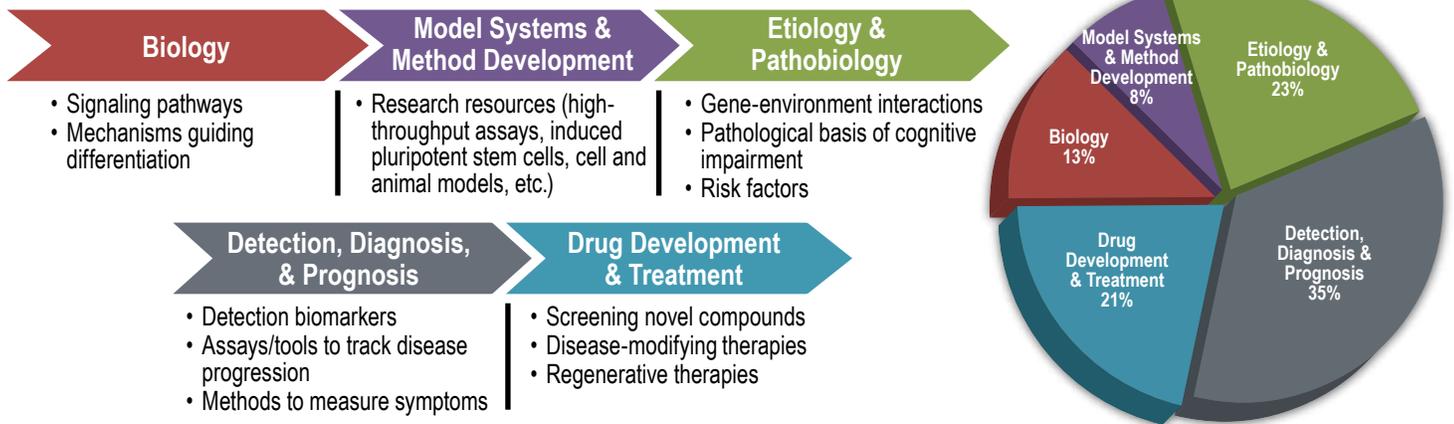
### **Bruce Bebo, Ph.D., National MS Society, Programmatic Panel Member**



# Program Portfolio

## RESEARCH SPECTRUM

Consistent with our knowledge and the state of MS and in order to meet our program's vision, the program has funded research along the entire disease research spectrum. Analysis of the most recently funded research projects (FY13-FY17) is reflected in the graph below, indicating the percentage of the MSRP's research investment in each area: a quarter towards understanding the disease etiology and pathobiology, a third for detection and diagnosis, a quarter for drug development and treatment, and a smaller portion toward understanding the biology and developing models and methods.



Although research in many of these research areas does not immediately produce or test new treatments, these investigations are critically important because they can reveal molecular targets that can lead to new treatments. MSRP-funded studies to develop models and understand the biology and etiology of MS have led to significant advances in the field. Examples of successful MSRP efforts in each of the research areas are presented in the next pages.

## RESEARCH OUTCOMES

From FY09 to FY17, the MSRP funded 91 awards, totaling \$51.1M. MSRP-funded research projects have resulted in numerous impactful outcomes, including 98 publications in high-impact, peer-reviewed journals and data-sharing at many scientific and patient-focused conferences.

Many MSRP grants are exploratory in nature, supporting the initial exploration of innovative, high-risk/high-gain, and potentially groundbreaking concepts in the MS research field, with the goal to generate preliminary data for future avenues of scientific investigation. MSRP-funded investigators have been awarded 38 follow-up research grants from other federal and non-federal funding agencies, including the National Institutes of Health (NIH), NMSS, and other non-profit organizations, totaling over \$27M to build on and advance knowledge gained from their MSRP-funded studies.



| Pilot Clinical Trials  |  |
|--|--|
| Ellen Mowry, M.D.,<br>Johns Hopkins University                         | <b>NCT02988401</b> : Evaluate whether insulin is safe and tolerable in people with MS and can improve their cognition.   |
| Kottil Rammohan M.D.,<br>University of Miami, Coral Gables             | <b>NCT03266965</b> : Define strategies that will raise histamine levels in the brain to overcome fatigue.  |
| Joseph Finkelstein, M.D., Ph.D.,<br>Columbia University Medical Center | <b>NCT03230903</b> : Assess the feasibility and impact of an innovative home-based physical telerehabilitation model in MS patients with significant mobility impairment.            |
| Leigh Charvet, Ph.D.,<br>New York University School of Medicine        | <b>NCT03499314</b> : Evaluate the efficacy of a remotely supervised platform to enhance hand rehabilitation in individuals living with progressive MS with reduced manual dexterity. |

# Investigations Across

## Finding ways to restore system functionality or mitigate symptoms

**Intranasal Insulin for Improving Cognitive Function in Multiple Sclerosis – Dr. Ellen Mowry, Johns Hopkins University:** To date, there are limited treatment options for MS patients who have symptoms of cognitive impairment. While there is some thought that MS disease-modifying therapies may improve some aspects of cognitive functions, there are no definitive data to support this claim. Dr. Mowry received an FY15 Pilot Clinical Trial Award to evaluate whether intranasal insulin is safe and tolerable for MS patients and whether it can improve cognitive function in MS patients. The trial is still early in its recruitment phase (ClinicalTrials.gov, trial number **NCT02988401**), but preliminary information indicates that intranasal insulin is tolerated by the trial participants.

**Modified Flavonoids as Selective Inhibitors of Hylauronidases for the Promotion of Remyelination – Dr. Lawrence Sherman, Oregon Health & Science University:** Dr. Sherman has an FY16 Investigator-Initiated Research Award (IIRA) to synthesize and test novel inhibitors of hyaluronidases. Inhibitors that show promising results in cell culture studies will then be tested in animal models, including the Japanese macaque encephalomyelitis (JME) model that Dr. Sherman developed through his FY08 award. If successful, the culmination of these studies will be a unique set of chemical compounds that promote remyelination and limit demyelination. Dr. Sherman is hopeful that he will compile the evidence required to further evaluate at least one compound in future pre-clinical and clinical trials.

DRUG  
DEVELOPMENT  
AND TREATMENT

## Learning how and why the system fails in MS

**Mechanisms of Low Physical Work Capacity, Fatigue, and Reduced Mobility in Multiple Sclerosis – Dr. Bo Fernhall, University of Illinois at Chicago:** Dr. Fernhall received an FY17 Exploration - Hypothesis Development Award to study the causes of low physical work capacity (PWC) and fatigue symptoms in MS patients. He hypothesizes that autonomic dysfunction (i.e., impaired regulation of heart rate, blood pressure, and blood flow) could be a major contribution to these symptoms. He will evaluate autonomic function at baseline and during exercise in MS patients and healthy controls to identify possible causes for low PWC and fatigue in MS patients. Understanding symptom etiology is important for developing appropriate interventions that improve the quality of life for MS patients.

ETIOLOGY AND  
PATHOBIOLOGY

## Learning how the biological system works

**Hyaluronan Oligosaccharides for the Promotion of Remyelination – Dr. Lawrence Sherman, Oregon Health & Science University, and Dr. Paul Weigel, Oklahoma Health Sciences Center:** In FY09, Dr. Sherman teamed up with Dr. Paul Weigel at Oklahoma Health Sciences Center for a Synergistic Idea Award to study a component of the extracellular matrix called hyaluronan (HA), and its role in preventing remyelination in MS. They found that, when HA is degraded by a specific enzyme called a hyaluronidase, the resultant digestion products appear to inhibit the maturation of oligodendrocyte progenitor cells into myelin-producing oligodendrocytes.

**Microglia Activation in Neuropathic Pain During MS: Possible Therapeutic Target – Dr. Julie Olson, University of Minnesota Twin Cities:** Neuropathic pain, the feeling of pain in the absence of a pain stimulus, is a common symptom reported by nearly 50% of MS patients. However, the etiology, or cause, of neuropathic pain is not completely understood. Dr. Olson received an FY16 Exploration - Hypothesis Development Award to study whether activation of the resident immune cells of the CNS, called microglial cells, contributes to the development of neuropathic pain in mouse models of MS. Furthermore, she will test whether a novel inhibitor of microglia activation reduces neuropathic pain in the mouse models. These are important foundation studies that could lead to the development of a new therapeutic to treat neuropathic pain in human MS patients.

**Promoting Myelin Formation via Manipulation of Oligodendrocyte Cytoskeleton – Dr. Carmen Melendez-Vasquez, City University of New York:** With funding from an FY10 Concept Award, Dr. Melendez-Vasquez found that soft, brain-like matrices promote oligodendrocyte maturation and expression of myelin proteins, and that stiffer, disease-like matrices inhibit these processes. Furthermore, inhibiting stiffness signaling in oligodendrocytes via genetic knockout of myosin II resulted in an increased ability to remyelinate axons after damage in a mouse model of MS.

BIOLOGY

# the Research Spectrum

## DETECTION, DIAGNOSIS, PROGNOSIS

Finding ways to identify MS early and measure and predict its progression

**Neuronal Determinants of Motor Disability in MS – Dr. Roland Henry, University of California, San Francisco:** Dr. Henry received an FY13 Idea Development Award to develop quantitative magnetic resonance imaging (MRI) metrics and electrophysiology tools that reflect both structural and functional alteration in the motor system. To date, Dr. Henry has developed novel MRI and motor function assessment tools. His long-term goal is to use these tools to predict motor disability in MS patients and better assess disease state to better assess treatment efficacy.

## Developing laboratory methods and disease models

**Therapeutic Remyelination Strategies in a Novel Model of Multiple Sclerosis: Japanese Macaque Encephalomyelitis – Dr. Lawrence Sherman, Oregon Health & Science University:** Dr. Sherman has been leveraging funds from the CDMRP to advance the MS field since FY08. In FY08, when MS was still funded under the Peer Reviewed Medical Research Program, he received an IIRA to characterize a novel non-human primate model of MS. He found that JME occurs in both progressive and relapsing-remitting forms in genetically susceptible animals. Furthermore, Dr. Sherman concluded that JME is an excellent model of MS etiology and could be utilized to study interventions for remyelination failure. He has since become the Principal Investigator of an NIH-funded grant that aims to develop these animals into an international resource for MS investigators who aim to test new MS drugs in pre-clinical trials.

**Restorative Neuroimmunology in Experimental Models of Multiple Sclerosis via Directly Induced Neural Stem Cell Transplantation – Dr. Stefano Pluchino, University of Cambridge; Dr. Regina Armstrong, Uniformed Services University of the Health Sciences; and Dr. Frank Edenhofer, University of Wurtzberg:** Most therapeutic options currently available to MS patients target the relapsing-remitting form of the disease; very few are efficacious for progressive MS. Dr. Pluchino, Dr. Armstrong, and Dr. Edenhofer were awarded an FY14 Investigator-Initiated Partnership Award to identify the ideal source of stem cells for transplantation and further define their mechanisms of action in the context of MS pathophysiology. The team's most recent accomplishment includes demonstrating that induced neural stem cells (iNSC) injected into mouse models of chronic MS ameliorate neuroinflammation and improve function. The engrafted iNSC decreased specific inflammatory metabolites and induced an anti-inflammatory phenotype into immune cells. Understanding the interplay between engrafted iNSC and inflammation is a crucial step toward the possible future use of iNSC to treat progressive MS.

**Mechanical Properties of the Injured CNS: Implications for Remyelination and Axonal Repair – Dr. Carmen Melendez-Vasquez, City University of New York:** In FY17, Dr. Melendez-Vasquez received an Exploration – Hypothesis Development Award to further explore the mechanical properties of CNS tissue. She expects that acute, short-term lesions will be softer than healthy tissue, and that chronic, long-term demyelination will result in a persistent increase in the stiffness of the lesion environment. The goals of this study are to establish a defined model for the impact of stiffness surrounding demyelinated lesions on oligodendrocyte maturation and function and to develop methods to generate oligodendrocyte progenitor cells (immature oligodendrocytes) for transplantation. Dr. Melendez-Vasquez believes that the results of this study could lead to the design of bio-compatible materials supportive of neuronal and glial development. This information would primarily benefit MS patients with secondary–progressive disease, where therapies aimed at improving remyelination and promoting neuroprotection are urgently needed.

## MODEL SYSTEMS AND METHOD DEVELOPMENT



**Above:** John Platt's MS diagnosis led him to pursue physical fitness as rehabilitation therapy, as well as advocacy for MS research. In between lifting weights, running marathons, and advocating for the NMSS, he served multiple times as a consumer reviewer on MSRP peer review panels.  
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<https://cdmrp.army.mil>

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