

**CDMRP**  
Department of Defense



# Multiple Sclerosis Research Program



U.S. Army Medical Research and Materiel Command



# Congressionally Directed Medical Research Programs



**History** The Congressionally Directed Medical Research Programs (CDMRP) originated in 1992 via a Congressional appropriation to foster novel approaches to biomedical research in response to the expressed needs of its stakeholders—the American public, the military, and Congress.

CDMRP's introduction prompted a unique partnership of the public, Congress, and the military. Success in managing the initial Congressional appropriations in breast cancer research, combined with other advocacy movements and the need for focused biomedical research, catapulted the CDMRP into a global funding organization for cancer, military medical, and other disease-specific research.

The CDMRP has grown to encompass multiple targeted programs and has received over \$11.2 billion in appropriations from its inception through fiscal year 2016 (FY16). Funds for the CDMRP are added to the Department of Defense 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 application evaluation with both steps involving dynamic interaction between scientists, clinicians, and consumers. The first tier is a scientific peer review of applications that measures each application against established criteria for determining scientific merit. The second tier is a programmatic review conducted by the Programmatic Panel, an independent panel separate from the peer review panel. The Programmatic Panel compares applications to each other and makes recommendations for funding based on a balance between scientific merit, portfolio composition, and relevance to program goals.



## Participation of Consumers

A unique aspect of the CDMRP is the active participation, throughout the program's annual cycle, of persons living with the disease (i.e., consumers). From the unique perspective gained through personal experience, the consumers bring a sense of urgency and focus to all levels of decision making. Consumers work collaboratively with leading scientists and clinicians in setting each program's vision and mission, reviewing applications, and making final funding recommendations. They evaluate the impact of the research to individuals with the disease, as well as the needs of family members, caregivers, and the clinicians who treat them.

# Multiple Sclerosis Research Program

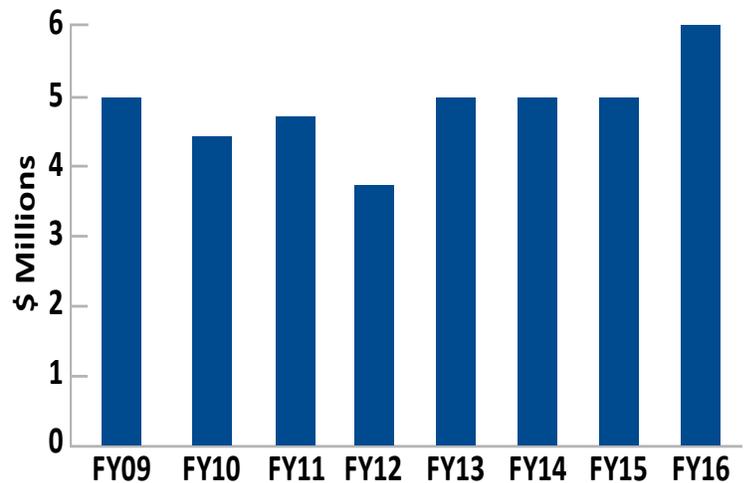
**Vision:** To prevent the occurrence, cure, reverse, or slow the progression, and lessen the personal and societal impact of multiple sclerosis

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

Multiple Sclerosis (MS) is a degenerative, chronic inflammatory disease of the central nervous system (CNS) that leads to cumulative neurologic disability over several years. Although MS affects over 400,000 individuals in the United States and about 2.1 million (M) individuals worldwide, its etiology and pathogenesis are largely unknown. While individuals of all ages are affected by MS, it is more commonly diagnosed in young adults, particularly women, between the ages of 20 and 40. Currently, there is no cure for MS.

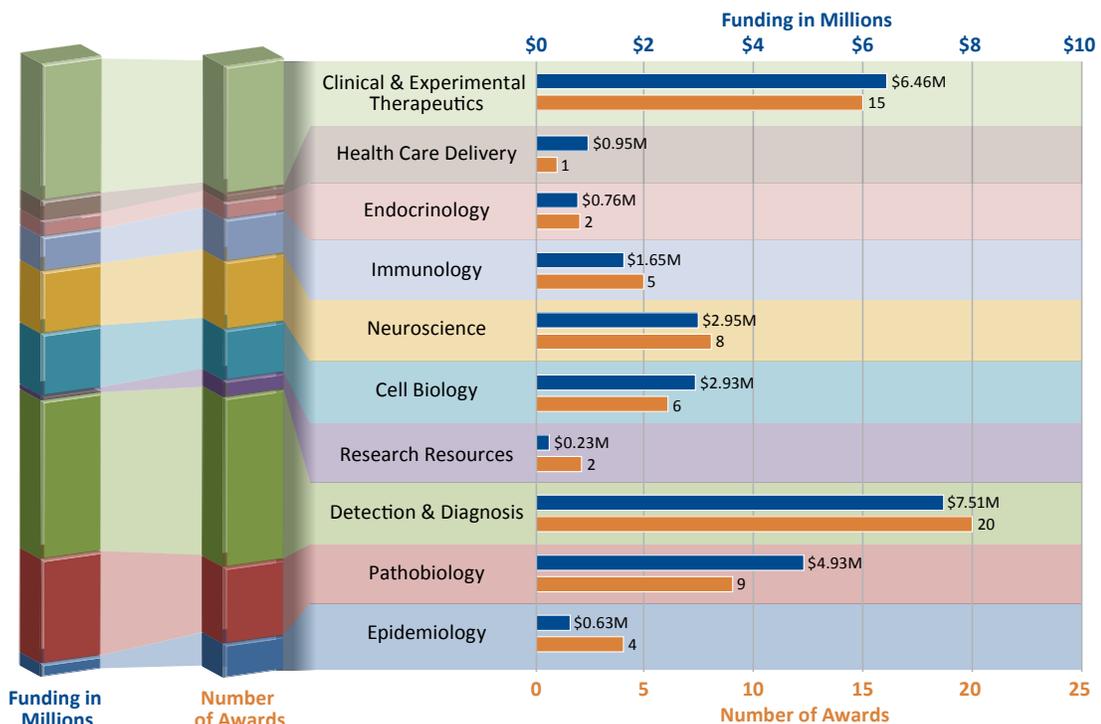
Congress first appropriated funds establishing the MSRP in FY09. Since then, a total of \$39.1M has been appropriated to the program, including \$6M in FY16.

## FY09–FY16 Congressional Appropriations



## MSRP Portfolio FY09–FY15

The portfolio is displayed as number of awards and amount of funding (in millions) for each research category



# Classifying Multiple Sclerosis

MS is a heterogeneous and unpredictable disease that can manifest in many ways across the MS patient population. The array of differences makes it critical that clinicians and researchers use well-defined descriptions of the different stages of the disease to communicate with patients, design and recruit for clinical trials, and make decisions about treatments.

A panel of MS experts convened in 2012 to review the current state of MS disease classifications, make recommendations for any classification changes, and identify areas that need research to move the field forward. The results of this meeting were published in the scientific journal *Neurology*.<sup>†</sup>

The panel made the following recommendations for classifying different stages of MS:

**1. Clinically Isolated Syndrome (new)** – It is the first clinical presentation of MS symptoms in a patient. When a patient presents with inflammatory demyelination coupled with brain magnetic resonance imaging (MRI) that reveals lesions, there is a very high likelihood that the patient will progress to MS.

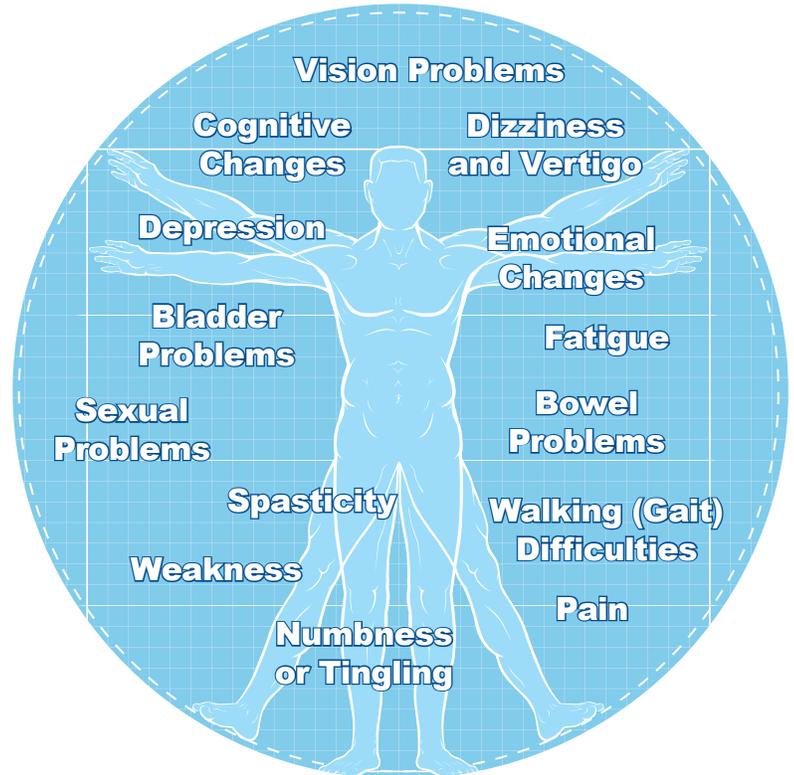
**2. Relapsing-Relapsing MS (RRMS)** – RRMS involves clearly defined periods of “activity,” when the neurologic symptoms of MS increase or new symptoms arise (the relapse), or there is activity detected by brain MRI. These periods of activity are followed by partial or complete recovery (remission).

**3. Progressive MS** – There are two progressive disease phenotypes: primary progressive MS (PPMS) and secondary progressive MS (SPMS). PPMS occurs when a patient sees a continuous, progressive accumulation of disability from the time they are first diagnosed. SPMS arises from the accumulation of disability that follows an initial period of RRMS; over time, there is less recovery between relapses, and the patient gradually develops the SPMS phenotype.

Phenotypes are defined not only in accordance with the general classification of disease but also by the current status of disease **activity** (active or not active) and state of **progression** (progressing or stable). Crucial information for determining the natural history of a patient’s disease activity and progression is obtained from MRIs performed regularly (at least annually in the case of RRMS).

Despite the advances in understanding MS, more research is still needed to determine the usefulness of imaging techniques and biomarkers for assessment of disease state and progression.

## Common Manifestations



### Less Common Manifestations:

Speech Problems, Swallowing Problems, Tremor, Seizures, Breathing Problems, Itching, Headache, Hearing Loss

The term **Progressive-Relapsing MS (PRMS)** is no longer used. Individuals who were previously diagnosed with PRMS are now considered to be primary progressive: active or not active.

<sup>†</sup> Lublin FD, Reingold SC, Cohen JA, et al. 2014. Defining the clinical course of multiple sclerosis: The 2013 revisions. *Neurology* 83: 278-286.

# Consumers and Researchers Working Together



## Through His Eyes

### John Platt, Consumer Peer Reviewer

My life's trajectory changed on an overcast September day in 2005 when I was told I had MS. My disease progressed rapidly during the first years following diagnosis. Two years after diagnosis, I was isolated and depressed, and felt as though I were a prisoner in my own body—destined for the wheelchair I had stored in my garage. Fortunately, my darkness was pierced by a National MS Society (NMSS) email inviting me to become an MS advocate, active in the society's various programs. My first-hand experience made me the leading expert on my MS, and I realized I could help others understand MS and its devastating impact. Today, I serve as the Chairman of the

NMSS's Pennsylvania Government Relations Committee.

I first learned about the MSRP through my participation with the NMSS. Taking ownership of my MS fueled my desire to serve as a Consumer Reviewer for the MSRP. It was apparent early on that everyone involved with the MSRP was dedicated to preventing the occurrence, curing, reversing, or slowing the progression, and lessening the personal and societal impact of MS. I was humbled by their knowledge, encouraged by their passion, and comforted by the fact that I wasn't alone. Not only did they care about me, but there was genuine care and compassion for the entire MS community. Possibly best of all, my voice was accepted as equal throughout the entire process.

Through my advocacy work, I have learned that like-minded individuals can work together to create a tidal wave of hope in the sea of change. As part of this tidal wave, the MSRP brings together the MS and scientific communities to create a productive partnership to fund research that will change the course of MS forever.



John completing the 2016 Boston Marathon

### Paul Drew, PhD – University of Arkansas Programmatic Panel Chair

"The CDMRP MSRP funds innovative research which addresses critical gaps in our knowledge concerning MS. The MSRP, in collaboration with other government and private agencies, is funding research which improves the lives of those affected by MS. It is an honor to be a part of the MSRP team of scientists, clinicians, and consumer reviewers dedicated to finding a cure for MS."



### Patrizia Casaccia, MD, PhD – Mount Sinai School of Medicine Scientific Peer Reviewer

"It was a wonderful and extremely rewarding experience to be part of the review process for MSRP, bringing scientists and MS patients together towards a common goal."

# Program Achievements

## **Roles for Dysfunctional Sphingolipid Metabolism in MS**

**Dr. Norman J. Haughey – Johns Hopkins University**

During the early stages of MS, demyelinated axons are able to remyelinate with some efficiency. However, this capability decreases over time, which leads to a transition from RRMS to the progressive stages of the disease. In response to demyelinating events, oligodendrocyte progenitor cells mature into the myelinating cells, oligodendrocytes. In FY10, Dr. Haughey received an Idea Award to investigate the mechanisms that drive the formation of new oligodendrocytes, and to learn the conditions that lead to remyelination failure.



Myelin is enriched in particular classes of lipid known as ceramides, sphingomyelins, and sulfatides. Comparison of the lipid composition in white matter of normal brain tissues to white matter in remyelinated brain tissues revealed key differences in the compositions. These differences in lipid composition change the repulsive force between layers of myelin, preventing the myelin from compacting into a tight and stable structure, analogous to the force that pushes two magnets away from each other. Dr. Haughey and his team believe that this disruption in the myelin structure makes the myelin more susceptible to future demyelinating events, and does not sufficiently support the underlying axon, which degenerates over time. Their work has identified an enzyme that is highly reactive to the inflammatory state that occurs during a demyelinating event. Work with an animal model of MS showed that inhibition of this enzyme partially restores the lipid composition during remyelination, allowing “new” myelin to compact around axons forming a more stable structure.

The preliminary data collected in this award lay the foundation for developing a biomarker panel capable of distinguishing RRMS from SPMS in humans, and has identified an enzyme target for therapeutic development. Current research in the Haughey laboratory is focused on identifying and developing small molecule therapeutics to restore myelin compaction.

2010

## **Dr. Brett Lund, University of Southern California Keck School of Medicine**

Demonstrated the importance of the Renin-Angiotensin System (RAS) in MS progression. He also found that an anti-inflammatory drug that activates the regulatory arm of RAS, if administered before damage to the CNS occurs, delays MS progression in mice. These studies provide strong evidence for developing MS therapeutics that target the RAS.

2013

## **Dr. Ralph Suarez, Children’s Hospital, Boston**

Developed and tested a method for “passive” functional MRI brain mapping in pediatric MS patients. This provides a new imaging method for patients too ill to actively participate in testing.

2012

## **Dr. Michael Moore, Tulane University**

Created a system for studying MS in laboratory cultures of nerve cells generated from induced pluripotent stem cells. He verified that these cells maintain their normal functions, and made progress understanding the capabilities and limitations of the system. This system could be used for rapid, high-throughput screening of potential MS treatments.

2011

## **Dr. Carmen Melendez-Vasquez, City University of New York, Hunter College**

Found that increased elasticity in the extracellular matrix promotes oligodendrocyte differentiation. Increasing brain elasticity by genetic knockout of myosin II fibers in mice increased their ability to remyelinate axons after chemically induced brain damage. This suggests that known inhibitors of myosin-II contractility might be useful in treating MS in humans.

2010

## **Dr. Yanming Wang and Dr. Robert Miller, Case Western Reserve University**

Synthesized an imaging probe and developed positron emission tomography (PET) imaging methods to selectively visualize myelinated nerves in a mouse model. This technique could be used to monitor disease progression and myelin repair in both humans and experimental animals.

2009



Target/Drug Discovery



Drug Development



Methods and Models



Imaging

2012

**Dr. Seth Smith, Vanderbilt University Medical Center**

Developed novel, high-resolution MRI techniques to image MS lesions in brain gray matter. For the first time, ongoing human trials demonstrate that the technique is capable of capturing chemical changes that occur during demyelination.

2011

**Dr. David Pleasure, University of California, Davis**

Discovered that administering PEDF, a multifunctional protein with neurotrophic properties, enhanced CNS remyelination and preserved CNS axons in mice with MS, while loss of the PEDF gene accelerated nerve damage and loss.

2011

**Dr. John Letterio, Case Western Reserve University**

Identified two compounds that activate the protein Nrf2, which normally regulates the body's response to oxidative damage. Testing one of these compounds in mice resulted in suppression of MS. These promising results suggest that targeting Nrf2 may be useful in treating MS in humans.

2010

**Dr. Youhai Chen, University of Pennsylvania**

Designed, synthesized, and tested 179 novel inhibitors of the regulatory protein c-Rel. Nine of these were found to reduce or prevent MS in mice. It is hoped that the best of these nine candidates will advance to clinical trials in human MS patients.

2009

**Dr. Stephen Elledge, Brigham and Women's Hospital**

Developed a novel high-throughput sequencing technology to identify self-targeting antibodies unique to MS patients. A novel autoantigenic motif was found in samples from MS patients that could be utilized as a disease marker or a target for therapeutics.

2012

**In Vivo Imaging of Cortical Inflammation and Subpial Pathology in MS by Combined PET and MRI**

**Dr. Caterina Mainero – Massachusetts General Hospital**

Dr. Mainero received an FY12 Idea Award to evaluate inflammation and structural tissue changes in the cortex of patients with RRMS. Previous work in the field indicated that a certain type of demyelinating brain lesions, called cortical lesions, are potential biomarkers of MS. Further evidence suggested that, when activated, ubiquitous immune cells found in the brain (microglia) may cause inflammation that leads to demyelinating lesions. For this project, Dr. Mainero is using advanced MRI techniques (7 Tesla [T] MRI) that she developed to study the structural changes in the MS patients' brains, in combination with PET techniques that can quantify microglia activation.



Using the 7T MRI techniques she developed, Dr. Mainero was able to identify the localization of cortical lesions, which is a critical development as even slightly less advanced MRI techniques are unable to observe these lesions. The PET imaging studies were the first to directly observe inflammation at the lesion sites in MS patients. Preliminary results of these studies revealed a correlation between the structural and inflammation characteristics of the observed lesions and the disease state of the patients (i.e., progressive versus relapsing-remitting disease). These results could be developed into tools for assessing cortical disease in MS patients.



For more information, visit

<http://cdmrp.army.mil>

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