



# Multiple Sclerosis Research Program



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



# Congressionally Directed Medical Research Programs



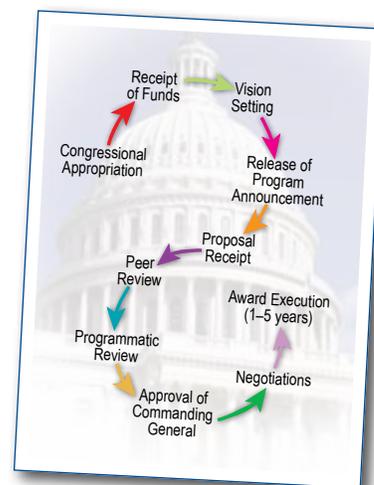
**History** The Office of the Congressionally Directed Medical Research Programs (CDMRP) was created in 1992 from a powerful grassroots effort led by the breast cancer advocacy community that resulted in a congressional appropriation of funds for breast cancer research.

This initiated a unique partnership among the public, Congress, and the military. The success in managing the initial congressional appropriations in breast cancer research combined with additional advocacy movements and the need for focused biomedical research catapulted the CDMRP into a global funding organization for cancer research, military medical research, and other disease-specific research.

The CDMRP has grown to encompass multiple targeted programs and has received over \$8 billion in appropriations from its inception through fiscal year 2014 (FY14). 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 application evaluation, with both steps involving dynamic interaction between scientists and clinicians—subject matter experts—and consumers. The first tier of evaluation is a scientific peer review of applications measured against established criteria for determining scientific merit. The second tier is a programmatic review, conducted by the Integration Panel (IP), which compares applications to each other and makes funding recommendations based on scientific merit, portfolio balance, and relevance to program goals.



## Consumer Advocacy Participation

A unique aspect of the CDMRP is the active participation of consumer advocates or patient/survivor representatives throughout the program's annual cycle. Consumers work collaboratively with leading scientists and clinicians in setting the MSRP's vision and mission, reviewing applications, and making final funding recommendations. From the unique perspective gained through personal experience, the consumer brings a sense of urgency and focus to all levels of decision making. Consumers evaluate the impact of the research to individuals with MS, as well as the needs of their family members, caregivers, and clinicians who treat them.

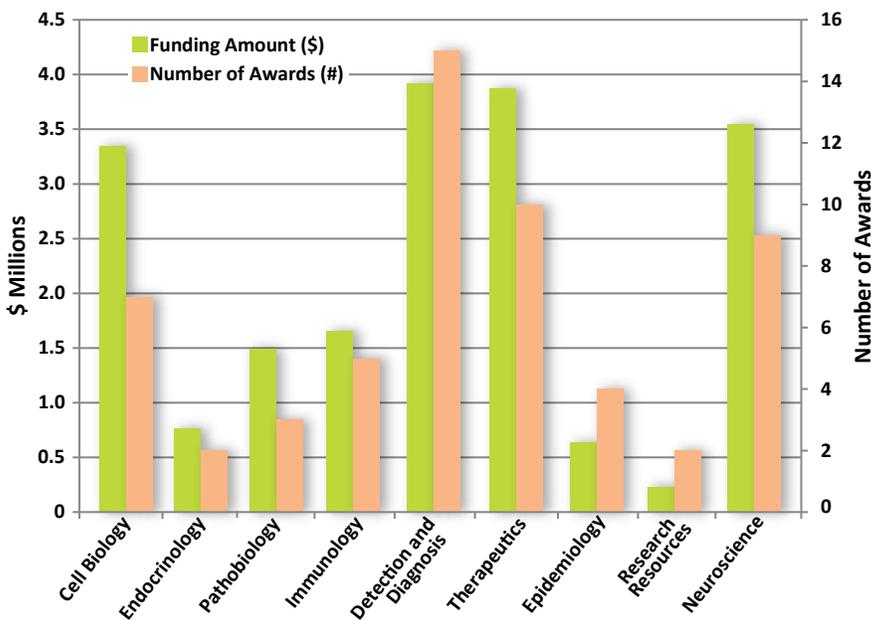
# Multiple Sclerosis Research Program

**Multiple sclerosis (MS)** is a degenerative, chronic inflammatory disease of the central nervous system 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.

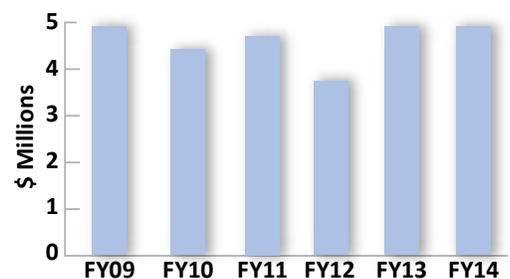
## History of the MSRP

In FY09, Congress first appropriated funds for the establishment of the MSRP at the CDMRP. Annual appropriations from FY09 through FY14 total \$28.1M, including **\$5M in FY14**.

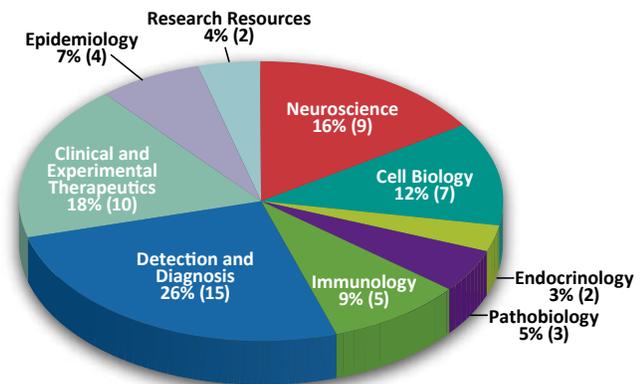
FY09–FY13 MSRP Research Portfolio



FY09–FY14 Appropriations



FY09–FY13 MSRP Research Portfolio by Percentage of Total Number of Awards (n=57)



MSRP AWARD MECHANISMS

<b>Metric Development and Validation (FY09) Award:</b> To support the development of readily accessible, cost-effective, validated analytical methods to quantify the disease, monitor disease progress, and evaluate the efficacy of new disease therapies.	<b>9 Awards</b> <b>\$1.4M</b>
<b>Synergistic Idea (FY09) Award:</b> To support the scientific collaborations between two to four multidisciplinary Principal Investigators to promote innovative ideas and novel, synergistic approaches to address a critical problem or question in MS research.	<b>12 Awards</b> <b>\$3.0M</b>
<b>Concept (FY10, FY11) Award:</b> To support the exploration of a highly innovative new concept or untested theory that addresses an important problem relevant to MS.	<b>14 Awards</b> <b>\$1.6M</b>
<b>Idea (FY10–FY13) Award:</b> To support conceptually innovative, high-risk/potentially high-reward research that could ultimately lead to critical discoveries in understanding the causes and progression of MS and/or improvements in patient care and/or quality of life.	<b>22 Awards</b> <b>\$13.4M</b>
<b>Investigator-Initiated Partnership (FY14) Award:</b> To support the development of translational research collaborations among no more than three independent investigators who will synergistically combine their unique skills and expertise to address a central problem or question in MS.	<b>TBD</b>

# Multiple Sclerosis

## Types of MS

**Relapsing-Remitting MS (RRMS):** The most common—disease course is characterized by clearly defined attacks (also called relapses or flare-ups) of worsening neurologic function followed by partial or complete recovery periods (remissions), during which symptoms improve partially or completely and there is no apparent progression of disease. About **85% of people with MS are initially diagnosed with RRMS.**

**Secondary-Progressive MS (SPMS):** This course follows after the RRMS course. Most people who are initially diagnosed with RRMS will eventually transition to SPMS, which means that the disease will begin to progress more steadily (although not necessarily more quickly), with or without relapses.

**Primary-Progressive MS (PPMS):** PPMS is characterized by steadily worsening neurologic function from the beginning. Although the rate of progression may vary over time with occasional plateaus and temporary, minor improvements, there are no distinct relapses or remissions. About **10% of people with MS are diagnosed with PPMS.**

**Progressive-Relapsing MS (PRMS):** The least common—is characterized by steadily progressing disease from the beginning and occasional exacerbations along the way. People with this form of MS may or may not experience some recovery following these attacks; the disease continues to progress without remissions.

## Common Manifestations



### Less Common Manifestations:

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

# Multiple Sclerosis Research Program

## Scientists and Consumers Serve Critical Roles

### **Craig Carpenter, Paralyzed Veterans Association Consumer Peer Reviewer**

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



### **Robert Fox, M.D., Cleveland Clinic, Mellen Center Scientific Peer Reviewer**

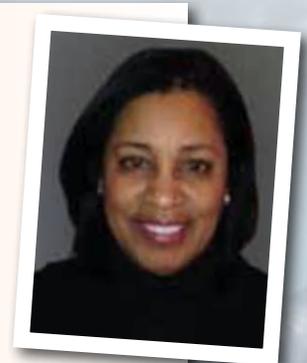
“This year’s CDMRP MSRP award will provide vital funding to build and develop translational research partnerships. These partnerships will join basic science and clinical researchers together, and also bring together researchers who have not previously been involved in MS research. This will provide an important opportunity to develop projects that directly connect basic research on MS with the clinical target – MS patients who need therapies. Consumer advocates are an important component of the CDMRP MSRP review process, as they ensure a clinical relevance and grounding to the proposed projects.”



Photo courtesy of the Cleveland Clinic

### **Nancita Rogers, National Multiple Sclerosis Society IP Consumer Reviewer**

“It is an incredible honor and privilege to serve on the IP, which is where recommendations for funding are made, as well as recommendations for the direction or focus of the research program. It is where I have an opportunity to explain how MS affects me, and the people who’ve been kind enough to trust me to share their stories. Through my time on the IP, I’ve had a chance to meet and work beside some of the country’s best MS researchers, doctors, etc. and share my experiences living with MS. Through my advocacy work, I get to see that there really is an effort to cure MS and improve quality of life for MSers.”



### **Timothy Coetzee, Ph.D., National Multiple Sclerosis Society IP Chair**

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



# Research Highlights

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



Dr. Sherman

**Larry Sherman, Ph.D., Oregon Health & Science University**

**Paul Weigel, Ph.D., Oklahoma Health Sciences Center**

Multiple sclerosis (MS) is a degenerative disease of the central nervous system characterized by the destruction of myelin sheaths, which are structures that insulate nerve cell fibers for optimal conduction of electrical impulses. Over the course of the disease, MS patients progressively lose the ability to remyelinate the damaged myelin. This is due, in part, to the gradual loss of oligodendrocyte progenitor cells' (OPCs) ability to mature into myelin-producing oligodendrocytes.



Dr. Weigel

In FY09, Drs. Larry Sherman and Paul Weigel were awarded an MSRP Synergistic Idea Award, the intent of which is to support synergistic and multidisciplinary approaches to address a central critical problem or question in MS research. Dr. Sherman had already discovered that a high molecular form of hyaluronan (HA), one of the chief components of the extracellular matrix, accumulates in demyelinated lesions in MS patients, which led him to hypothesize that degrading the accumulated HAs via hyaluronidases (enzymes that break down HA) may promote remyelination. Unexpectedly, when the HAs were degraded in this fashion, the byproducts of some hyaluronidases prevented OPC maturation, leading Dr. Sherman to further hypothesize that specific hyaluronidases expressed in demyelinating lesions and their degradation products may be blocking OPC maturation.

With MSRP support, Dr. Sherman teamed up with Dr. Weigel, a leading expert in the field of HA biochemistry, to assess whether OPCs in demyelinating lesions, gathered from rodents with experimental autoimmune encephalomyelitis, express specific hyaluronidases and whether the byproducts of these enzymes are implicated in inhibiting OPC maturation. Results indicated that OPCs expressed several hyaluronidases, including HYAL1, HYAL2, and PH20. Interestingly, HA digestion products formed by PH20, but not the others, inhibited OPC maturation and thus prevented remyelination, signifying PH20 as a promising molecular target for promoting remyelination in MS and other demyelinating diseases. Based on these findings, Drs. Sherman and Weigel aim to identify drugs that specifically inhibit PH20 hyaluronidase activity as a potential therapeutic for promoting remyelination in MS patients.

*Preston M, Gong X, Su W, Matsumoto SG, Banine F, Winkler C, Foster S, Xing R, Struve J, Dean J, Baggenstoss B, Weigel PH, Montine TJ, Back SA, Sherman LS. 2013. Digestion products of the PH20 hyaluronidase inhibit remyelination. Ann Neurol 73:266-280.*



**Charles Guttman, M.D., Brigham and Women's Hospital, IP Member**

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

# Research Highlights

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



Dr. Givogri



Dr. Moyano

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

MS is a potentially debilitating autoimmune disease of the central nervous system (CNS) that leads to damage to the myelin (demyelination) of nerve cells, which results in disruptions in the ability of nerves to communicate with one another. As the disease progresses, patients gradually lose the ability to repair damaged nerves, causing the physical and/or mental disabilities associated with MS. The mechanisms associated with the failure to repair the damaged myelin in MS are unknown, but these are thought to involve many factors including defective differentiation of neural stem cells and oligodendrocyte progenitor cells into mature oligodendrocytes (the cells responsible for myelin repair). Current methods for the diagnosis of MS can involve the evaluation of physical symptoms and imaging of the CNS. While blood tests can be used to rule out other diseases, none can yet confirm a diagnosis of MS.

In FY10, Dr. Maria Irene Givogri received an Idea Award from the MSRP to determine whether sulfatides—a class of glycolipids that have been shown to be in abundance in the myelin of nerves and are thought to play a major role in the upkeep of myelin—could be used to identify demyelination related to MS. While sulfatides are known to be important regulators of autoimmunity, their presence in the plasma of MS patients had not yet been studied. With MSRP support, Drs. Givogri and Ana L. Moyano compared sulfatide levels in the plasma of 14 Relapsing-Remitting MS (RRMS) patients to 14 healthy controls, and they observed potentially clinically relevant results. Plasma levels of specific types of sulfatides

correlated with the severity of the patient's relapse as defined by the Expanded Disability Status Scale for MS patients, and also with the age and time since the patient's last relapse. These findings suggest that plasma levels of sulfatides may reflect demyelination damage associated with MS attacks and may serve as a potential biomarker for the diagnosis and prognosis regarding MS. With recent reports showing higher incidence rates of MS in the military population, the importance of improved diagnostics is critical for the timely detection and treatment of MS.

Dr. Givogri and her group continues their research through this award to better understand the release of sulfatides from myelin after MS attacks and their role as a regulator of myelin repair in MS. Their goals are to determine how sulfatides affect the growth and regulation of the cells responsible for myelin repair to better understand the loss of myelin repair associated with MS. With this information, they not only want to find better methods for diagnosing MS, but they also hope to find potential therapies for people suffering from MS.

*Moyano AL, Pituch K, Li G, van Breemen R, Mansson JE, and Givogri MI. 2013. Levels of plasma sulfatides C18 : 0 and C24 : 1 correlate with disease status in relapsing-remitting multiple sclerosis. J Neurochem 127(5):600-604.*

### **Nancy Sicotte, M.D., Cedar-Sinai Medical Center, Los Angeles MSRP-Funded Principal Investigator**

"The DOD funding was important in establishing a collaboration between Dr. Shi and myself. From this foundation, we have expanded our work together utilizing novel imaging strategies to detect MS-related disease effects, including depression and cognitive impairment, on key brain structures. We are working to validate these new imaging biomarkers to monitor MS disease progression and to serve as outcome measures in clinical trials of remyelinating and neuroprotective therapies."

*Gold SM, O'Connor MF, Gill R, Kern KC, Shi Y, Henry RG, Pelletier D, Mohr DC, and Sicotte NL. 2014. Detection of altered hippocampal morphology in multiple sclerosis-associated depression using automated surface mesh modeling. Hum Brain Mapp Jan;35(1):30-7.*



## MISSION

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



For more information, visit

<http://cdmrp.army.mil>

or contact us at:

[usarmy.detrick.medcom-cdmrp.mbx.cdmrp-public-affairs@mail.mil](mailto:usarmy.detrick.medcom-cdmrp.mbx.cdmrp-public-affairs@mail.mil)

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