CDMRP

Department of Defense

Multiple Sclerosis Research Program





U.S. Army Medical Research and Materiel Command

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. Since then, the CDMRP has grown to encompass multiple targeted programs and has received nearly $7 billion in appropriations from its inception through fiscal year 2012 (FY12). 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.

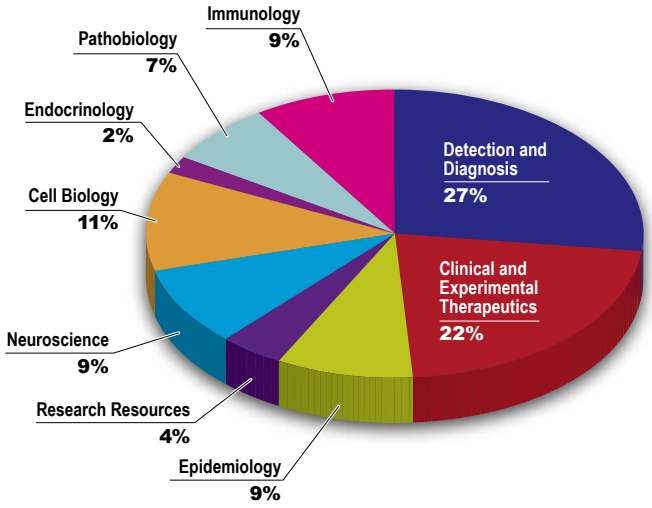
Application Review Process

The CDMRP uses a two-tier review process for application evaluation with both tiers involving dynamic interaction among scientists and consumer advocates (disease survivors). 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, which is composed of leading scientists, clinicians, and consumer advocates. The Integration Panel compares applications to each other and makes recommendations for funding based on scientific merit, portfolio composition, and relevance to program goals.

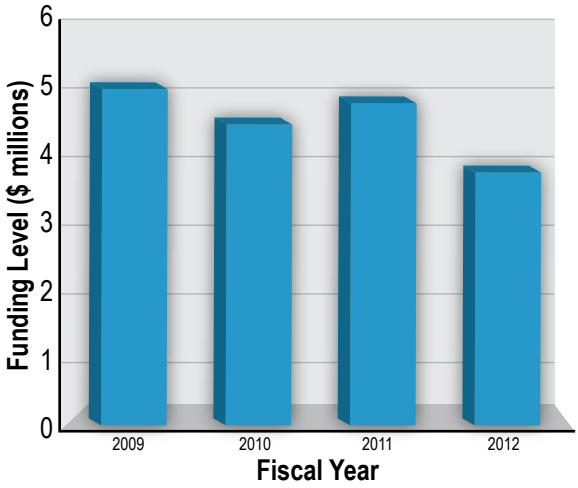
Timothy Coetzee, Ph.D.
National Multiple Sclerosis Society
FY12 Integration Panel Member
"In order for us to stop MS in its tracks, restore lost function, and end MS forever it will take the collaborative efforts of researchers around the world. The MSRP is a great example of a program that brings committed scientists together to find solutions."

Multiple Sclerosis Research Program

Since its inception in FY09 through FY12, the MSRP has invested more than $18.1 million in supporting innovative and impactful research that addresses fundamental issues and gaps in MS. The MSRP examines the research landscape and, knowing the funding gaps, utilizes its investment strategy for the greatest impact for the research community and the American public. The FY09–FY11 MSRP research portfolio, which includes 45 awards, is depicted as follows.



FY09–FY11 MSRP Portfolio by Research Area



FY09–FY12 Congressional Appropriations

Jorge Oksenberg, Ph.D.
University of California, San Francisco
FY12 Integration Panel Chair

"What we hope to accomplish with the MSRP is to secure critical support for audacious scientists dedicated to basic and translational discovery in multiple sclerosis research. The Integration Panel brings together neuroscientists, clinicians, and patient advocates to select a handful of outstanding grant proposals from an extraordinarily rich pool of applications. The task to recommend for funding what constitutes great and innovative science is not easy, and our discussions can be as interesting (and lengthy) as the best proposals. The frustration to leave many meritorious applications not recommended for funding is inescapable, only mitigated by the hope that the chosen research projects will be truly transformative and discover new diagnostics, treatments, and maybe a cure for multiple sclerosis."

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 that leads to cumulative neurologic disability over the years. Although MS affects more than 400,000 individuals in the United States and about 2.1 million individuals worldwide, its etiology and pathogenesis are largely unknown. Moreover, the progression, severity, and specific symptoms of MS are unpredictable and vary from person to person. 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.

There are four subtypes of MS based on patterns of disease progression[1].

Relapsing-Remitting MS (RRMS): RRMS is the most common disease course characterized by clearly defined attacks (relapses) of worsening neurologic function followed by partial or complete recovery periods (remissions). Approximately 85% of people with MS are initially diagnosed with RRMS.

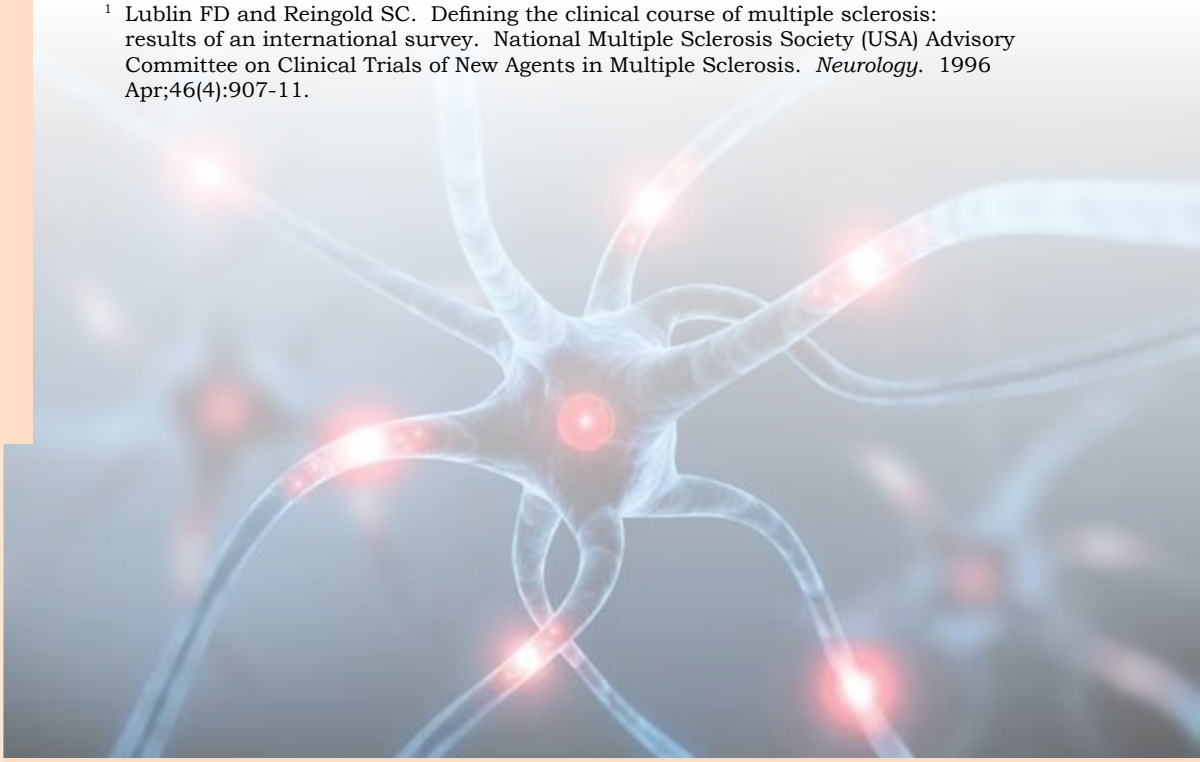
Secondary-Progressive MS (SPMS): SPMS follows an initial period of RRMS where the disease begins to worsen more steadily with or without occasional relapses, slight remissions, or plateaus.

Primary-Progressive MS (PPMS): PPMS is characterized by steadily worsening neurologic function from onset without distinct relapses or remissions.

Progressive-Relapsing MS (PRMS): PRMS is the least common disease course characterized by continuous neurologic decline from onset with occasional relapses but without remissions.

[1] Lublin FD and Reingold SC. Defining the clinical course of multiple sclerosis: results of an international survey. National Multiple Sclerosis Society (USA) Advisory Committee on Clinical Trials of New Agents in Multiple Sclerosis. *Neurology*. 1996 Apr;46(4):907-11.

Nancita Rogers
Consumer
National Multiple Sclerosis Society
FY12 Integration Panel Member
"It has been an incredible honor to serve as a consumer member on the MSRP Integration Panel. It was frightening at first, but I quickly learned that the multidisciplinary scientists and clinicians really want to get to the bottom of MS. They really listen and value input from people like me living with this disease. This program is young but has already begun to bear fruit; grantees are introducing or improving on products and ways to diagnose, monitor, and treat MS that did not exist 3 to 4 years ago. They are looking at symptoms and potential treatments that were not in the forefront such as cognitive dysfunction, disease progression, including primary and secondary MS, possible remyelination, and genetics. Their work, in my opinion, jump-starts the process of understanding what causes MS, contributes to improved quality of life, and perhaps gets us that much closer to a cure in my lifetime."



Program Highlights

Imaging Metrics of White Matter Degeneration in Multiple Sclerosis

Nancy Sicotte, M.D., Cedars-Sinai Medical Center

Yonggang Shi, Ph.D., David Geffen School of Medicine, University of California, Los Angeles

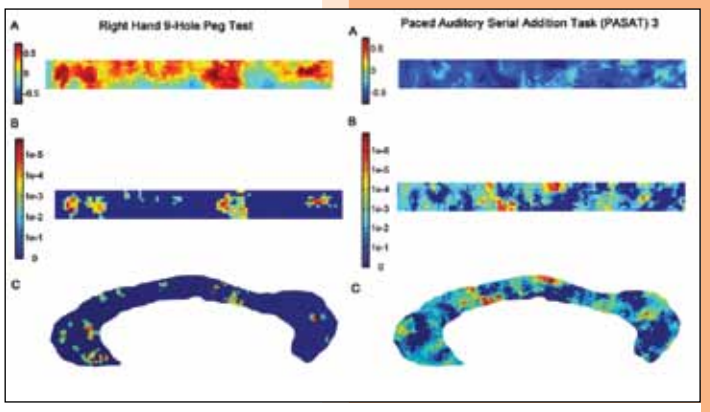
Nancy Sicotte, M.D.

Yonggang Shi, Ph.D.

Magnetic resonance imaging (MRI) of the brain is the primary imaging modality for diagnosing and monitoring MS. One of the limitations of using MRI in MS is the large variability of sensitivity and specificity due to the discordance between lesion location and clinical presentation in patients thus making MRI poorly indicative of clinical outcomes, such as relapse, impairment, and disability.

The corpus callosum (CC), the white matter structure that facilitates communication between the two hemispheres in the brain, may be damaged in the early stages of MS. Based on evidence that regional changes in the CC may be more closely linked with future disability than global central nervous system damage, Dr. Nancy Sicotte, with support from an FY09 MSRP Metric Development and Validation Award, aimed to develop and validate robust imaging metrics to localize and characterize changes in the CC in relation to clinical measures of MS disease progression. Specifically, Dr. Sicotte hypothesized that localized diffusion abnormalities in the CC measured by diffusion MRI would precede CC thinning and predict the worsening of associated functions in MS patients.

Previously, Dr. Yonggang Shi developed a novel, fully automated image analysis algorithm capable of analyzing large MRI data sets with high sensitivity that allows the joint analysis of both morphological and diffusion data. Using this algorithm, Dr. Sicotte analyzed serial MRIs performed on 28 RRMS patients and 15 controls. These data were collected every 6 months for 3 years. Dr. Sicotte and Dr. Shi assessed the regional diffusivity changes in CC in relation to clinical measurements of MS, such as right-hand dexterity and cognitive impairment (via Nine-Hole Peg Test and Paced Auditory Serial Addition Test, respectively). Results indicated that there were significant diffusivity differences between RRMS patients and controls localized to the posterior CC, including the splenium. Moreover, Dr. Sicotte found diffusivity changes in distinct CC regions associated with worsening right-hand dexterity (transcallosal sensory cortical areas) and worsening cognitive impairment (frontal and parietal cortical regions). These results demonstrated that changes in regional CC diffusivity are more sensitive predictors of clinical progression than CC atrophy and may be promising imaging-based biomarkers for monitoring MS disease progression and treatment response.



MS effects are localized to specific regions of the corpus callosum (CC)

This figure represents the CC abnormalities that were identified using the automated image analysis algorithm. The algorithm identified and localized abnormal diffusion properties in the white matter tracts that make up the CC in relation to specific clinical measures such as right-hand dexterity (9-hole peg test) and cognitive function (PASAT).

Row A: Overall correlations overlaid on a standardized grid. Row B: Statistically significant areas of abnormality overlaid on a standardized grid. Row C: Statistically significant areas overlaid on an actual map of the CC. The left column shows the results from the 9-hole peg test, which identified MS-associated damage to areas of the CC that connect sensory and motor regions from both hemispheres. The right column shows results from PASAT, where poor performance was related to changes in pathways that mediate attention and processing speed.

Carmen Melendez-Vasquez, Ph.D.

Promoting Myelin Formation via Manipulation of Oligodendrocyte Cytoskeleton

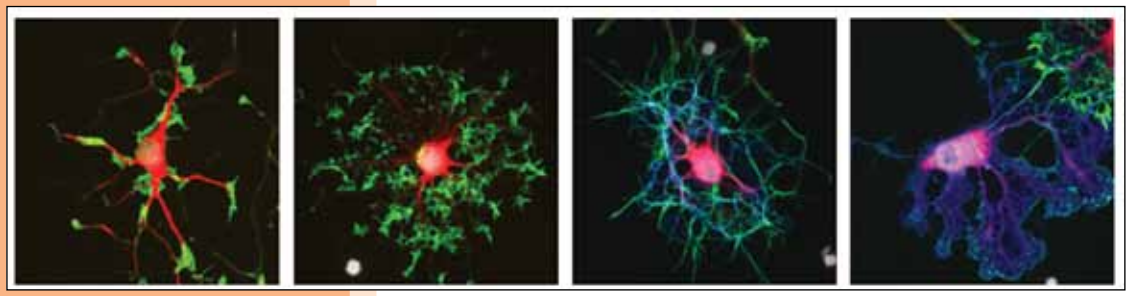
Carmen Melendez-Vasquez, Ph.D., City University of New York, Hunter College

MS is characterized by an autoimmune attack on myelin sheaths, causing demyelination of the axons and subsequent disruptions in nerve transmission. Myelin repair is mediated by oligodendrocytes, which are cells responsible for myelin production. Oligodendrocyte progenitor cells (OLPs) are recruited into areas of MS lesions and differentiate into mature oligodendrocytes, which remyelinate the axons and restore nerve function. However, oligodendrocyte differentiation and remyelination become less efficient over the course of the disease, leading to cumulative damage to the central nervous system. The underlying mechanisms of myelin repair inhibition are largely unknown.

Previously, Dr. Carmen Melendez-Vasquez found that myosin II (a key regulator of cellular actin assembly and contractility) activity of OLPs inversely correlated with the ability to differentiate and produce myelin. While differentiating into mature oligodendrocytes, OLPs' actin cytoskeleton undergoes extensive remodeling, including extension of multiple branches that eventually give rise to myelin-producing structures. Myosin II is largely responsible for controlling this cytoskeleton remodeling and does so by responding to the mechanical properties of the cell's microenvironment (i.e., the extracellular matrix [ECM]). Due to scar tissue formation, ECM of MS lesions tends to be stiffer and less elastic than that found in normal brain tissue. Dr. Melendez-Vasquez hypothesizes that the stiffness of the ECM in MS lesions may be inhibiting OLP differentiation and remyelination in a myosin II-dependent manner.

With support from an FY10 MSRP Concept Award, Dr. Melendez-Vasquez first assessed whether ECM stiffness affects the cytoskeletal changes required for OLP differentiation in vitro. Results demonstrated that OLPs grown in soft (i.e., normal brain-like) ECM more readily formed cytoskeletal branches and produced more myelin basic protein than OLPs grown in stiff (i.e., MS lesion-like) ECM, indicating that ECM stiffness indeed plays a significant role in OLP differentiation and myelin repair.

Next, Dr. Melendez-Vasquez assessed whether myosin II inhibition can promote OLP differentiation and remyelination of induced focal demyelinating lesions in mice engineered to lack myosin II in their oligodendrocytes. Interestingly, evidence of remyelination was observed as early as 7 days after injury. Encouraged by these results, Dr. Melendez-Vasquez is extending her studies into inflammatory models that more closely resemble MS pathology. Results of her work may lead to novel therapeutic strategies for promoting neuroregeneration and myelin repair in MS patients.



A composite showing the development of oligodendrocyte progenitors in culture from less mature (left panel) to mature (right panel). This sequence shows very nicely the changes in the cytoskeleton of the cells. Red: tubulin, green: actin, blue: myelin basic protein, and white/grey: nuclei.

From Doctor to Patient to Advocate

Phil Posner, Ph.D.

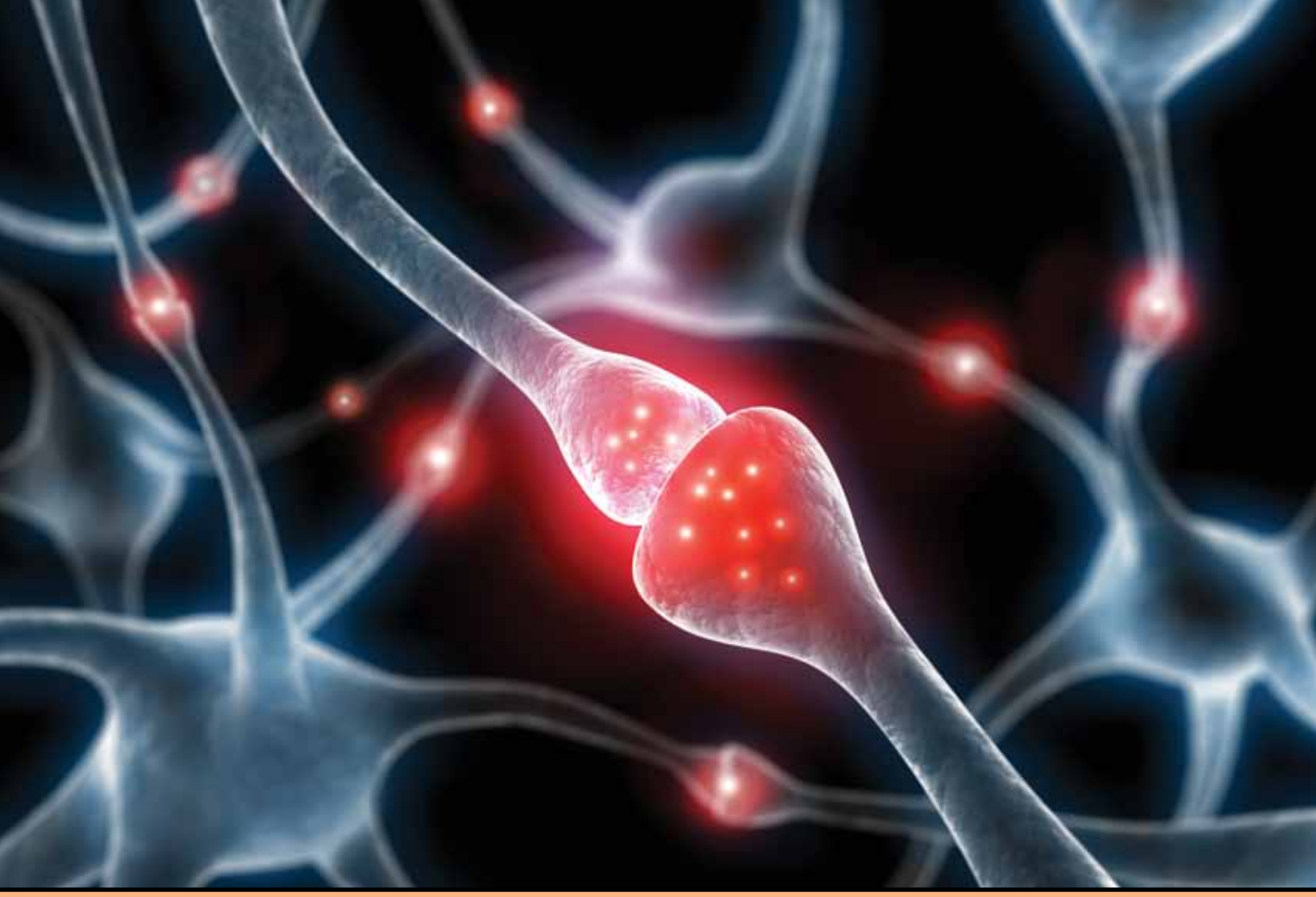
Knowing about MS and some of its symptoms is one thing. Being diagnosed with MS is completely different and leads to a new awareness of the illness along with a newfound respect of learning. Phil Posner, a neuroscience instructor who has a Ph.D. in medical sciences, is intimately aware of the differences.

Phil Posner, Ph.D.

"I had book knowledge of multiple sclerosis and also had three friends with relapsing-remitting multiple sclerosis. I tried to stay abreast of MS issues in order to help my friends." He first noticed possible MS symptoms in 1986, but the neurologist who examined him in England did not seem concerned. His symptoms were atypical of MS patients. Once the diagnosis of MS was confirmed, two aspects of his life did not change—Phil's dedication to advocacy work and his commitment to other MS patients. Having worked with organizations for many years, Phil was presented with a new opportunity in 2006 when he and his wife moved to Northern Virginia. He attended a regional health fair, met officials from the National Capital Chapter of the National MS Society, volunteered to help, and has not looked back.

In 2011, Phil was nominated as a peer reviewer for the MSRP. He was familiar with research review panels because of his background, and he quickly found the interest and energy to examine and discuss many different proposals. "There is an amazing dialogue that takes place integrating the science with the practicality of the problems faced by the consumer reviewers," Phil said. "Both the scientists and the consumer reviewers learn from each other. I personally have learned much valuable information from the proposals we review as well as from the other panel members with MS and the scientists on the panel."

"When I meet other people who have MS, I always listen to their stories," Phil said. "Everyone is different. I have learned that there are a lot of people, young and old, who need help with various life issues. I have learned how rewarding it is to be able to help, and I have learned how much a little support for someone can add to the quality of his or her life."



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http://cdmrp.army.mil
or contact us at:
CDMRP.PublicAffairs@amedd.army.mil
301-619-7071
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