DoD Multiple Sclerosis Research Program (MSRP)

Each year, the Department of Defense's office of the Congressionally Directed Medical Research Programs (CDMRP) assesses scientific opportunities to advance research in specific areas. The investigators supported by individual programs are making significant progress against targeted diseases, conditions, and injuries. This list is not intended to be a full representation of accomplishments, but rather a sampling of the broad portfolio of research and advances resulting from congressional appropriations.

Year	MSRP Research Contributions	Additional Information and Hyperlinks
2009	Dr. John Chen developed a myeloperoxidase-targeted magnetic resonance imaging (MRI) agent (myeloperoxidase-gadolinium) for the detection of early, preclinical, and subclinical disease activity (both with and without treatment) in an experimental autoimmune encephalomyelitis mouse model of multiple sclerosis.	• MSRP Research Highlight
2009	Dr. Nancy Sicotte developed a metric modeling morphometry of the corpus callosum with diffusion tensor imaging to study changes in relapsing-remitting multiple sclerosis.	• Gold SM, O'Connor MF, et al. 2014. Detection of altered hippocampal morphology in multiple sclerosis-associated depression using automated surface mesh modeling. Hum Brain Mapp 35(1):30-7.
2009	Drs. Yanming Wang and Robert Miller developed a near-infrared fluorescence imaging technique capable of direct quantification of myelination in vivo.	• MSRP Research Highlight
2009	Dr. Stephen Elledge and his team developed a new technology that combines synthetic biology and DNA sequencing—Phage Immunoprecipitation Sequencing (PhIP-Seq). This new technology identifies novel MS-specific autoantigens in hopes of finding new therapeutic targets for treating MS.	• MSRP Research Highlight
2009	Dr. Larry Sherman and Dr. Paul Weigel found that digestion products of a particular enzyme, PH20 hyaluronidase, inhibit oligodendrocyte progenitor cell (OPC) maturation, which is a necessary process for neuron remyelination. Identifying PH20 as a promising molecular target has the potential to lead to therapeutics to promote remyelination in MS patients.	• MSRP Research Highlight
2009	Drs. Damien Pearse and Paul Dalton created and fully characterized nanoparticles that specifically target spinal lesions in a rat model of MS. Furthermore, when these targeted nanoparticles were loaded with the anti-inflammatory drug Rolipram, both behavioral and histological disease progression slowed.	• Führmann T, Ghosh M, et al. 2015. Peptide-functionalized polymeric nanoparticles for active targeting of damaged tissue in animals with experimental autoimmune encephalomyelitis. Neurosci Lett 602:126-32.
2009	Dr. Jonathan Alexander identified endothelial microparticle biomarkers of MS stress and injury. These findings, when correlated with iron deposits found in particular regions of the brain, indicate that failure of the blood-brain barrier may precede the immune infiltration and neurodegeneration observed in MS patients.	• Alexander JS, Chervenak R, et al. 2015. Blood circulating microparticle species in relapsing-remitting and secondary progressive multiple sclerosis. A case-control, cross-sectional study with conventional MRI and advanced iron content imaging outcomes. J Neurol Sci 355(1-2):84-89.

Year	MSRP Research Contributions	Additional Information and Hyperlinks
2010	Dr. Maria Irene Givogri studied the plasma sulfatide levels of MS patients to determine if they could serve as a diagnostic of MS-related demyelination. She observed that specific types of sulfatides correlated with the severity of a patient's relapse, and his/her age and time since last relapse.	• MSRP Research Highlight
2010	Dr. Brian Zabel identified that a small molecule, 2-(α-naphthoyl) ethyltrimethyl ammonium iodide (α-NETA), inhibits the interaction between chemerin and its receptor, chemokine-like receptor 1 (CMKLR1). This inhibition prevents immune cell migration to the brain and delays the onset of symptoms in a mouse model of MS.	• MSRP Research Highlight
2010	Dr. Youhai Chen designed, synthesized, and tested a total of 179 new compounds as potential therapeutics to treat primary and/or secondary progressive MS. A number of these compounds were found to significantly inhibit the autoimmune response and reduce disease severity in a mouse model of MS. Further preclinical studies on the top 9 candidates, or their analogs, will explore their potency, metabolism, pharmacokinetics, and developability properties.	
2010	Dr. Norman Haughey was able to use the preliminary data gathered from this award to develop a biomarker panel capable of distinguishing RRMS from SPMS in humans, and has identified an enzyme target suitable for therapeutic development.	
2010	Dr. Carmen Melendez-Vasquez demonstrated that chemical ablation of myelin II promoted brain elasticity, and that this increased elasticity in turn promoted oligodendrocyte progenitor differentiation. As small molecule inhibitors of myelin II already exist, this is a promising new therapeutic target to alleviate disease burden in MS patients.	• Wang H, Rusielewicz T, et al. 2012. Myosin II is a negative regulator of oligodendrocyte morphological differentiation. J Neurosci Res 90(8):1547-56. • Rusielewicz T, Nam J, et al. 2014. Accelerated repair of demyelinated CNS lesions in the absence of non-muscle myosin IIB. Glia 62(4):580-91.
2011	Dr. Sheng-Kwei Song developed an advanced MRI technology called diffusion basis spectrum imaging (DBSI). DBSI models tissue water diffusion in and around nerve axons, providing a clear picture of nerve health without other cellular interference. This advanced technology enhances the use of imaging for diagnosing MS and tracking the efficacy of potential treatments.	• MSRP Research Highlight
2011	Dr. Michael Moore successfully obtained highly enriched populations of neuronal cells from induced pluripotent stem cells, and refined the culture conditions necessary to maintain cell viability and optically stimulate and record cellular functions. Furthermore, he made excellent progress understanding the capabilities and limitations of the system.	• Huval RM, Miller OH, et al. 2015. Microengineered peripheral nerve-on-a-chip for preclinical physiological testing. Lab Chip 15(10):2221-32.

Year	MSRP Research Contributions	Additional Information and Hyperlinks
2011	Using a mouse model of MS, Dr. David Pleasure found that recombinant PEDF enhanced oligodendroglial survival and regeneration in toxin-demyelinated corpus callosum. Furthermore, intravenous administration of recombinant PEDF delayed the onset, decreased peak severity, and diminished long-term spinal cord dorsal axon loss and neurological deficits in this model system.	• Sohn J, Selvaraj V, et al. 2012. PEDF is a novel oligodendrogenic morphogen acting on the adult SVZ and corpus callosum. J Neurosci 32(35):12152-64.
2011	Dr. John Letterio identified two lead triterpenoids that strongly activated Nrf2, a protein that typically regulates a cell's response to oxidative stress. Using one of the triterpenoids to treat a mouse model of MS resulted in effective disease suppression.	
2012	Dr. Seth Smith developed a novel battery of quantitative MRI methods with sufficient resolution and sensitivity to characterize differences in cortical gray matter between healthy volunteers and patients with MS.	• Dula AN, Pawate S, et al. 2016. Magnetic resonance imaging of the cervical spinal cord in multiple sclerosis at 7T. Mult Scler 22(3):320-28.
2012	Dr. Henry Roland has developed a high-resolution spinal cord imaging MRI protocol and test-retest experiments to evaluate reliability of estimating spinal cord grey and white matter segments.	• Schlaeger R, Papinutto N, et al. 2015. Association between thoracic spinal cord gray matter atrophy and disability in multiple sclerosis. JAMA Neurol 72(8):897-904.
2012	Dr. Caterina Mainero has developed 7T MRI techniques to identify the localization of cortical lesions, a first for the field.	• MSRP Research Highlight • Mainero C, Louapre C, et al. 2015. A gradient in cortical pathology in multiple sclerosis by in vivo quantitative 7 T imaging. Brain 138(Pt 4):932-45. • Louapre C, Govindarajan ST, et al. 2015. Beyond focal cortical lesions in MS: An in vivo quantitative and spatial imaging study at 7T. Neurology 85(19):1702-09.
2012	Dr. Ralph Suarez developed a functional MRI method of passively mapping brain function in pediatric study participants.	• Suarez RO, Taimouri V, et al. 2014. Passive fMRI mapping of language function for pediatric epilepsy surgical planning: validation using Wada, ECS, and FMAER. Epilepsy Res 108(10):1874-88.
2013	Dr. Brett Lund characterized expression levels of key components in the renin-angiotensin-system (RAS) in the spinal chord and brain of EAE mice at different disease stages. He also found that an anti-inflammatory drug that activates the regulatory arm of RAS, if administered early enough in the disease progression, could delay MS progression in mice.	