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) was born 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 triggered the initiation of a unique partnership among the public, Congress, and the military, which has grown to encompass multiple targeted programs. Funds for the CDMRP are added by Congress to the Department of Defense budget annually to provide support for targeted research programs focused on a variety of cancers, genetic diseases, trauma-induced problems, childhood diseases, and other areas of health interest to military personnel and their families, the veteran population, and the general public. Under the auspices of the U.S. Army Medical Research and Materiel Command (USAMRMC), the CDMRP manages these programs, from receipt of funds through competitive selection of proposals and individual project performance to award closeout.
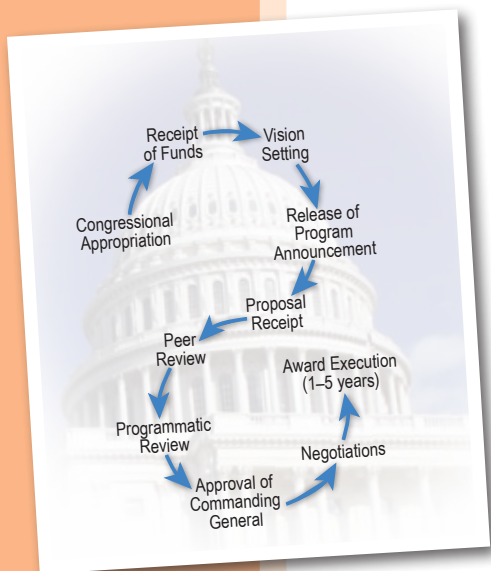
Consumer Advocate Participation

Consumer advocates (disease survivors, or family members) actively participate throughout the annual cycle, including setting the program's vision, participating in the peer review of proposals, and contributing to the funding decision process. Their firsthand experiences with the disease provide a unique perspective that helps scientists understand the human side of how research will impact their community.

Proposal Review

The CDMRP program management cycle includes a two-tier review process for proposal evaluation recommended by the National Academy of Sciences' Institute of Medicine. Each level of review is conducted by members of panels composed of scientists and clinicians who are subject matter experts and consumers. The first tier of evaluation is an external scientific peer review of applications against established criteria for determining scientific merit. The second tier is a programmatic review conducted by members of an Integration Panel who compare submissions and make funding recommendations based on programmatic priorities and mechanism-specific criteria. The Commanding General of USAMRMC issues the final approval for funding.

Fiona Hoey
National MS Society
Consumer Peer Reviewer
"I have an enormous amount of respect for the people who work the bench daily to eradicate (or ease) multiple sclerosis, so when they thank me for my involvement in the review process I am taken aback! Here I am, in awe of them and what they do, and the fact that they respect and listen to the consumer perspective floors me. But, it is also what makes the program so special. Consumers are giving something to the scientific community by offering glimpses of their life. A lab rat could never do that."

Multiple Sclerosis Research Program

Multiple sclerosis (MS) is a chronic neurological disease of unknown etiology that is associated with both physical and cognitive impairment. Although more common in young adults, particularly women, individuals of all ages have been diagnosed with this debilitating disease. The Multiple Sclerosis Research Program (MSRP) challenges the scientific community to design innovative research that will increase the understanding of the etiology and pathogenesis of MS and improve assessment and treatment options.

Focus Areas

The MSRP specifically encourages applications that address critical needs of the MS community and concentrate on any of the following areas:

- *Biological Basis of Disease Progression*
  - Primary progressive MS
  - Transition from relapsing/remitting to secondary progressive MS
  - Long-term stable disease with low disability
- *Risk Factors (Identification and Modification) Leading to Prevention of MS*
  - Microbial influences
  - Hormonal influences
  - Nutritional influences
  - Other environmental influences
- *Biomarkers for Preclinical Detection of MS*
- *Drug Discovery*
  - Assay development
  - Screening of novel compounds
  - Predictors of treatment response
- *Biological Basis of Fatigue, Sexual Dysfunction, Cognitive Impairment, Affective Disorder, and Rehabilitation*

Through offering a variety of award mechanisms, the MSRP plans to fund a broad research portfolio of innovative translational and preclinical studies.

Jorge Oksenberg, Ph.D., University of California, San Francisco
**Integration Panel Chair**
"As a young funding program, MSRP is still developing and sharpening its identity, but it is already evident that this program is fulfilling a very important role in supporting transformative basic and translational research in the field of multiple sclerosis. The short-, medium-, and long-term objective of all the participants in the MSRP is to reduce the impact of multiple sclerosis. We understand that the urgency of developing successful interventions is paramount; progress may look slow at times, but it is steady and promising. Understanding the roots of MS is within our grasp."

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.
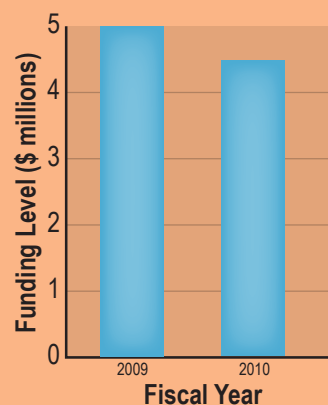
Imaging

In Vivo Gradient Echo Plural Contrast Imaging to Measure CNS Damage and Differentiate MS Subtypes

Anne Cross, M.D.
Washington University in St. Louis
Metric Development and Validation Award

Objective: Evaluate a new magnetic resonance imaging technique, Gradient Echo Plural Contrast Imaging as a method to discern the extent and severity of tissue pathology in MS.

Long-term goal: Develop a new noninvasive, readily available, and easily implemented imaging method to monitor the severity of the tissue damage underlying individual MS lesions, and develop an improved imaging endpoint for future clinical trials of new therapeutic agents for MS.

Myeloperoxidase Imaging for Early Lesion Detection and Treatment Tracking

John Chen, M.D., Ph.D.
Massachusetts General Hospital
Metric Development and Validation Award

Objective: Establish and validate a new magnetic resonance imaging contrast agent, bis-5HT-DTPA-Gd (MPO-Gd), to noninvasively track and quantify myeloperoxidase (MPO) activity in early subclinical active inflammatory demyelinating lesions in a mouse model of multiple sclerosis.

Long-term goal: Establish MPO-Gd imaging as a quantitative metric to detect early subclinical disease multiple sclerosis activity and track the effectiveness of therapy.

Development and Validation of an fMRI Pain Metric for MS

Heather Wishart, Ph.D.
Dartmouth College
Metric Development and Validation Award

Objective: Create a functional magnetic resonance imaging (fMRI) pain metric and determine the relationship between augmented central pain processing and self- and clinician-administered pain measures.

Long-term goal: Develop and test a minimally invasive, graded fMRI probe specific for evaluating pain experienced by patients with MS to facilitate studies on the neurobiological basis and treatment of MS-associated pain.

Voxel-Wise Time-Series Analysis of Quantitative MRI in Relapsing-Remitting MS: Dynamic Imaging Metrics of Disease Activity Including Prelesional Changes

Aaron Field, M.D., Ph.D.
University of Wisconsin, Madison
Metric Development and Validation Award

Objective: Validate the "preactive" lesion hypothesis in MS by identifying the spatiotemporal imaging signature of white matter destined to undergo acute, focal inflammation and demyelination using a longitudinal magnetic resonance imaging (MRI) data set.

Long-term goal: Clarify which of the currently available MRI-based metrics are most meaningful in monitoring disease activity that will help to identify, characterize, and predict the formation and evolution of nascent MS lesions before they appear on conventional imaging to facilitate appropriate clinical decisions.

William MacNally
National MS Society
Consumer Peer Reviewer
"The first time [at peer review] is kind of scary—I really wasn't sure if I did it right, and would the smart people in the room get really turned off by what I have to say, and is my contribution really worthwhile. You get to the end and—WOW!—they all tell you what a great contribution you made ... They really want to know what you think and why! You really learn something and, most of all, you have HOPE for the future because there are all these really smart people out there thinking about what to do about MS."

In Vivo Imaging of Myelination for Drug Discovery and Development in Multiple Sclerosis

Yanming Wang, Ph.D.
Robert Miller, Ph.D.
Case Western Reserve University
Synergistic Idea Award

Objective: Use positron emission tomography (PET) and a carbon-11-labeled myelin-imaging ligand, (E,E)-1-(4'-aminostyryl)-4-(4'-aminomethylstyryl)-2,5-dimethoxy-benzene ([11C] CIC) and histology to quantify myelin injury and repair in animal models of MS after treatment with selected therapeutic agents.

Long-term goal: Utilize PET imaging to quantify local levels of myelination and repair processes in demyelinating conditions such as MS, to quantitatively evaluate the efficacy of therapeutic agents aimed at promoting remyelination.
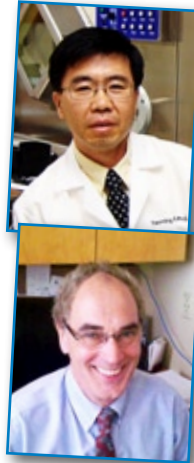
Disease Assessment

Disability-Specific Symptom Inventory Short Forms to Improve MS Outcome Assessment

Carolyn Schwartz, Sc.D.
DeltaQuest Foundation, Inc.
Metric Development and Validation Award

Objective: Use data from a nationwide sample of over 1,000 MS patients to improve and further develop the Symptom Inventory (SI), a self-report measure of impairment that contains 99 items aimed at tracking brain lesion-related impairment, by applying modern psychometric methods and theory to existing and new data sets.

Long-term goal: Produce reliable, valid, and responsive short forms of the SI for patient-reported assessment of impairment in MS, which will enable clinicians and researchers to quantify and monitor disease progress, and evaluate the efficacy of disease therapies.

Imaging Metrics of White Matter Degeneration in Multiple Sclerosis

Nancy Sicotte, M.D.
University of California, Los Angeles
Metric Development and Validation Award

Objective: Model serial changes in the corpus callosum (CC), which is a critical white matter structure connecting the hemispheres of the brain preferentially impacted early in the course of MS. Determine the relationship between focal thinning (measured using previously collected longitudinal brain imaging data) to changes in diffusion tensor metrics (measured using an imaging technique sensitive to subtle changes in nerve fibers) and determine the clinical significance of these changes over time.

Long-term goal: Develop and validate imaging metrics to localize and characterize changes in the CC to measure MS disease progression.

David Wagner, Jr., Ph.D.
University of Colorado Denver and Health Science Center
**Scientific Peer Reviewer**
"Serving on the [MSRP] peer review panel has been a tremendous honor and has taught me a lot about this disease and the importance of finding treatments and ultimately a cure. The CDMRP provides an extremely important arm in the battle against MS and other autoimmune diseases. A unique perspective to this panel is the inclusion of consumer advocates, people who are suffering from MS. They provide important perspectives about where this program needs to go, i.e., find a cure, quickly! The consumer reviewers examine the same proposals as the scientific reviewers and make comments on how that particular research would affect their lives. This is extremely helpful to the scientists who can be excited about the science but lose sight of the ultimate goal—how will this research directly impact the life of a person suffering from this disease."

Biomarkers

MHC Peptide Tetramer Assay Validation for CD4+ T Cells in MS

Karen Cerosaletti, Ph.D.
Benaroya Research Institute at Virginia Mason
Metric Development and Validation Award
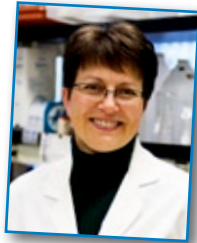
Objective: Generate major histocompatibility complex (MHC) class II peptide tetramers specific for MS autoantigens and evaluate the prevalence of tetramer-positive T cells across different stages of MS.

Long-term goal: Establish the necessary technological parameters for use of MHC class II tetramers as biometric tools for monitoring disease prognosis and progression, and for evaluating the response to therapy in multiple sclerosis.

Plasma Endothelial Microparticles in Multiple Sclerosis: A Novel Metric Assay of Disease Activity and Response to Treatment

Jonathan Alexander, Ph.D.
Louisiana State University Health Sciences Center
Metric Development and Validation Award

Objective: Determine whether monthly measurements of multiple plasma endothelial microparticle (EMP) and platelet microparticle populations, (pre- and post-treatment with interferons β1a and β1b) by multiple microparticle analysis profile (MMAP) accurately reflect and predict disease activity and oncoming relapses in MS patients.

Long-term goal: Employ MMAP as a novel biometric for detection, analysis, and determination of therapeutic responses to treatment with beta-interferon's to permit: (1) earlier, less expensive, and more objective prognosis of MS; (2) monitoring of MS disease activity, severity and progression longitudinal studies of MS; and (3) the measurement of therapeutic effectiveness.

Colleen Hayes, Ph.D.
University of Wisconsin, Madison
Integration Panel Member
"Only when we understand the multifaceted drivers of multiple sclerosis will we be able to envision how to eliminate the drivers, rather than to simply treat disease symptoms. Each of the Integration Panel members has thought deeply about what the future of MS research is. It was a great honor to join with my Integration Panel colleagues from other disciplines, and with consumer advocates, to rigorously debate where the interdisciplinary research breakthroughs might come, to articulate this vision, and to invest the resources in a portfolio of research with a high potential of yielding forward progress. There was a surprising degree of agreement among scientists, clinicians, and consumer advocates when all was said and done, because we took as much time as was needed to debate, explain, and clarify all points of view. The consumer advocates added a realistic, down-to-earth viewpoint that is helpful in the scientific debate. They rightfully insisted that the research be highly relevant to the problem of solving this very complex disease. Their participation kept the program highly focused."

PhIP-Seq for Autoantibody Profiling in MS

Stephen Elledge, Ph.D.
Brigham and Women's Hospital
Metric Development and Validation Award

Objective: Utilize Phage Immunoprecipitation Sequencing (PhIP-Seq), a sequencing technology used in combination with synthetic biological approaches in proteomics, to analyze the autoantibody profiles of MS patients and age/sex-matched controls, and identify novel MS-specific autoantigens.

Long-term goal: Categorize MS-specific autoantigens to elucidate new targets for tolerance induction therapy.

Therapeutics

Harnessing GPR17 Biology for Treating Demyelinating Disease

Nitin Karandikar, M.D., Ph.D.
Qing Lu, Ph.D.
University of Texas Southwestern Medical Center at Dallas
Synergistic Idea Award

Objective: Investigate whether G-protein coupled receptor 17 (GPR17) signaling activation results in blockade of remyelination in neuroinflammatory lesions.

Long-term goal: Develop novel therapeutic strategies for demyelinating disease using GPR17 as a target.

Gene-Environmental Interactions in Progression of Multiple Sclerosis

Murali Ramanathan, Ph.D.
Bianca Weinstock-Guttman, M.D.
Jun Qu, Ph.D.
Robert Zivadinov, M.D., Ph.D.
*State University of New York, Buffalo*
Synergistic Idea Award

Objective: Investigate the role of interactions between genes associated with MS risk and environmental factors such as cigarette smoking, vitamin D, and Epstein-Barr virus (EBV) infection, in the inflammatory and neurodegenerative pathophysiological processes that cause brain injury in MS.

Long-term goal: Identify the gene-environmental interactions that promote disease progression in MS to facilitate the development of new preventive and therapeutic interventions.

Hyaluronan Oligosaccharides for the Promotion of Remyelination

Larry Sherman, Ph.D.
Oregon Health & Science University
Paul Weigel, Ph.D.
University of Oklahoma Health Sciences Center
Synergistic Idea Award
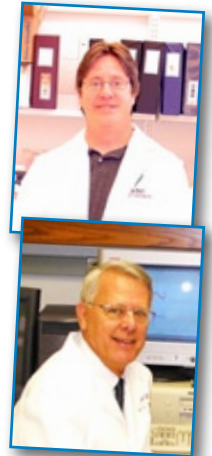
Objective: Identify the precise forms of hyaluronan (HA) that prevent remyelination, then, using this information, formulate specific molecules of HA that could be used to compete with the inhibitory forms found in MS lesions and therefore promote remyelination.

Long-term goal: Develop a novel therapeutic strategy to promote remyelination.

Site-Directed Nanotherapeutics to Abrogate RRMS and Promote Remyelination Repair

Damien D. Pearse, Ph.D.
University of Miami Miller School of Medicine
Paul Dalton, Ph.D.
Queensland University of Technology, Australia
*Synergistic Idea Award*

Objective: Generate a novel nanotherapeutic vehicle, nanoparticles that target the extracellular matrix/endothelial components and the myelin basic protein, for site-directed targeting to MS lesions.

Long-term goal: Develop a multifunctional therapeutic approach for preventing inflammation/demyelination and promoting plasticity for enhanced recovery after relapsing-remitting MS.

Binfeng Lu Ph.D., University of Pittsburgh
Scientific Peer Reviewer
"The MSRP offers additional funding mechanisms that provide enhanced support for MS research. Participating as an MSRP peer review panel member has been a wonderful experience for me. The quality of grant proposals was high and I had a great time reviewing them. Including consumer advocates in the peer review process is a good idea. Their participation helps balance good science and urgent patients' needs – this is particularly important for a Ph.D. scientist like me."
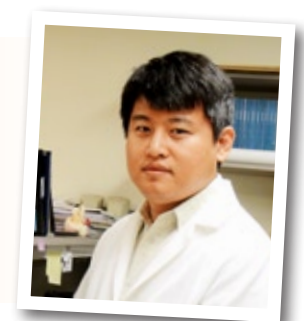
For more information, visit:
http://cdmrp.army.mil
or contact us at:
CDMRP.PublicAffairs@amedd.army.mil
301-619-7071

11-2010