

Multiple Sclerosis Research Program

Strategic Plan

INTRODUCTION

The Congressionally Directed Medical Research Programs (CDMRP) represents a unique partnership among the U.S. Congress, the military, and the public to fund innovative and impactful medical research in targeted program areas. In 2015, an ad hoc committee of the National Academies of Sciences, Engineering, and Medicine was assembled to evaluate the CDMRP’s two-tier review process and its coordination of research priorities with the National Institutes of Health (NIH) and the Department of Veterans Affairs (VA). As part of their final report,¹ the committee recommended that each CDMRP program “...develop a strategic plan that identifies and evaluates research foci, benchmarks for success, and investment opportunities for 3–5 years into the future,” and that these strategic plans “should specify the mission of the program, coordination activities with other organizations, research priorities, how those priorities will be addressed by future award mechanisms, how research outcomes will be tracked, and how outcomes will inform future research initiatives.”

In response to these recommendations, this document presents the current strategy for the CDMRP’s Multiple Sclerosis Research Program (MSRP). The MSRP Strategic Plan identifies the high-impact research goals most important to its stakeholders while providing a framework that is adaptable to changes in the medical research environment to address those goals. This plan has been formulated to provide greater clarity of the program’s goals over time to the public and other stakeholders. Funding for the MSRP is Congressionally appropriated on an annual basis; therefore, there is no guarantee of future funding. The MSRP Strategic Plan will be reviewed during the program’s annual Vision Setting meeting and updated as necessary.

MSRP BACKGROUND AND OVERVIEW

The MSRP was established in fiscal year 2009 (FY09) to support innovative and impactful research that addresses fundamental issues and gaps in multiple sclerosis (MS). Its Vision and Mission are as follows:

VISION: To prevent, 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 for the benefit of Service members, Veterans, and the American public

FUNDING HISTORY

MSRP began in FY09 with an appropriation of \$5 million (M). Since then, a total of \$45.1M has been appropriated to the program. Since FY09, 672 applications (598 projects) have been submitted, and 69 projects (82 awards) were funded from FY09-FY16. For certain collaborative projects, each collaborating Principal Investigator can receive a separate award so the number of distinct projects funded is less than the number of separate awards. Figure 1 shows FY09-FY17 appropriations and the awards made per year.

Figure 1. MSRP Appropriations and Numbers of Awards (Projects), FY09-FY17



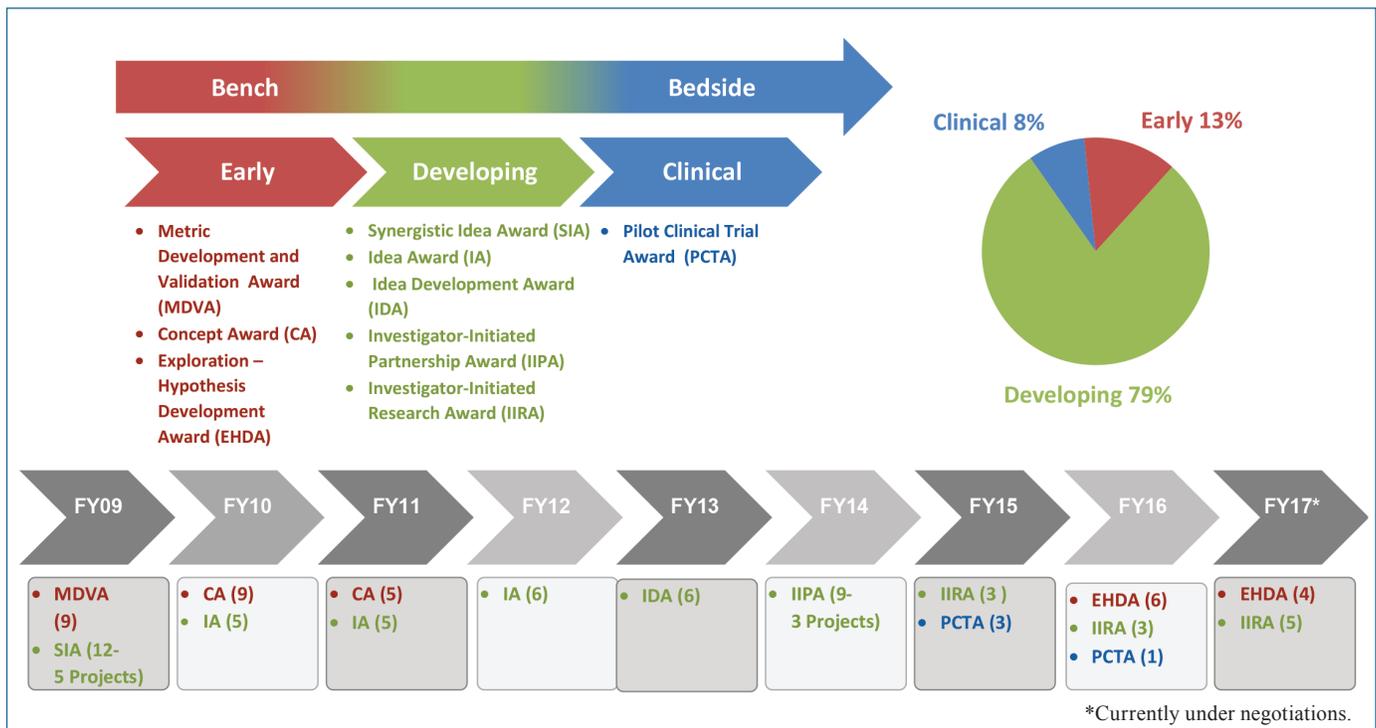
*Currently under negotiations.

INVESTMENT HISTORY

The MSRP's investment strategy has evolved to meet the needs of consumers and the scientific community.

Since its inception, the program has funded research projects along the continuum of research. The MSRP has offered a variety of award mechanisms to foster new ideas, encourage established scientists in the field, attract new scientific expertise to MS research, and promote multi-disciplinary collaborations. As shown in Figure 2, to date, 13 percent of funding has been allocated to support the exploration of new, untested concepts and ideas, with the goal of providing a foundation for future new research (e.g., through the Metric Development and Validation, Concept, and Exploration – Hypothesis Development Awards). Seventy-nine percent of funding has been allocated to support the development of more mature ideas to move them toward clinical application (e.g., through the Synergistic Idea, Idea, Idea Development, Investigator-Initiated Partnership, and Investigator-Initiated Research Awards). The remaining eight percent of the MSRP's research investment has been allocated to fund pilot clinical trials. The bottom half of Figure 2 below shows the types and numbers of the awards and projects (in parentheses) supported by these funds.

Figure 2. MSRP Investment Strategy, FY09-FY17



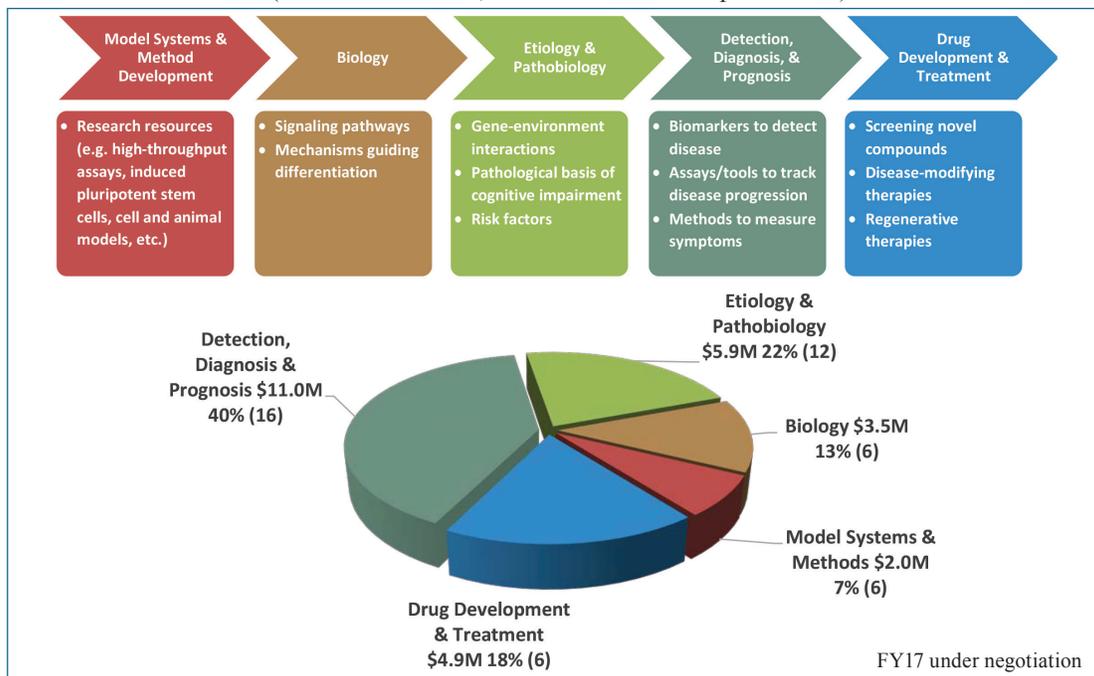
RESEARCH PORTFOLIO

Most recently, between FY12 and FY17, the MSRP has funded a wide variety of MS research projects along the disease research spectrum, including model systems, method development, biology, etiology, pathobiology, detection, diagnosis, prognosis, drug development and treatment. As shown in Figure 3, over one third of the total funding has been invested in detection, diagnosis, and prognosis, and nearly a quarter of the funding has been invested in MS etiology and pathobiology. Although more basic investigations into etiology, biology, and pathobiology do not directly produce or test new treatments, they are important because they reveal potential molecular targets for treatments that can be tested in more advanced research. Figure 3 below presents the alignment of MSRP funding along the disease research spectrum. The top half provides a description of the categories that make up the disease research spectrum, and the pie chart demonstrates the distribution of the portfolio investment across the disease spectrum.

RESEARCH ACCOMPLISHMENTS

MSRP research has resulted in a variety of impactful achievements that have furthered our understanding of MS etiology and pathobiology, identified targets for potential treatment, and developed tools for early detection/diagnosis. Examples of successful MSRP efforts in each of the research areas are presented here.

Figure 3. Program Priorities along the Disease Research Spectrum, FY12 – FY17
(Millions of dollars, number of awards in parenthesis)



Model Systems and Method Development

Dr. Michael Moore at Tulane University created a system for studying MS in laboratory cultures of nerve cells generated from induced pluripotent stem cells and verified that these cells maintain their normal functions. This system could be used for rapid, high-throughput screening of potential MS treatments (Huval RM, et al. 2015. Microengineered peripheral nerve-on-a-chip for preclinical physiological testing. *Lab Chip*. 15(10): 2221-2232).

Biology

Dr. Jeffrey Rothstein at Johns Hopkins University found that astrocytes respond in MS (and other) models of demyelination by a significant upregulation of the protein monocarboxylate transporter 1 (MCT1).

Etiology and Pathobiology

Dr. Ito Kouichi at Rutgers University identified a link between alterations in the gut microbiota and MS and highlighted the importance of gut microbiota in autoimmune disease progression. He identified that gut dysbiosis as one of the risk factors associated with the onset of central nervous system autoimmunity, which is generally believed to underlie MS (Yadav SK, et al. 2017. Gut dysbiosis breaks immunological tolerance toward the central nervous system during young adulthood. *PNAS*. 114(44): E9318–E9327).

Detection, Diagnosis, and Prognosis

Dr. Seth Smith at Vanderbilt University Medical Center developed novel assessments of cognition in MS patients. Three of the methods developed using 7T magnetic resonance imaging (MRI) assessed markers that correlated well with patient cognitive function. Two of the three methods have also been adapted to the more clinically accessible 3T MRI. These adapted methods are being used by other clinicians at other institutions (Dula AN, et al. 2015. Magnetic resonance imaging of the cervical spinal cord in multiple sclerosis at 7T. *Mult Scler*. 22(3): 320-328 (http://cdmrp.army.mil/msrp/research_highlights/17seth_smith_highlight).

Drug Development and Treatment

Dr. Brett Lund at the University of Southern California identified a promising new target for the treatment of MS. Using a mouse model of MS, he showed that the anti-inflammatory drug angiotensin 1-7 can slow progression of the disease. This drug has recently been formulated for human use and, if found to be beneficial in this population, could be fast-tracked, potentially reaching patients sooner than it would have otherwise (http://cdmrp.army.mil/msrp/research_highlights/17brett_lund_highlight).



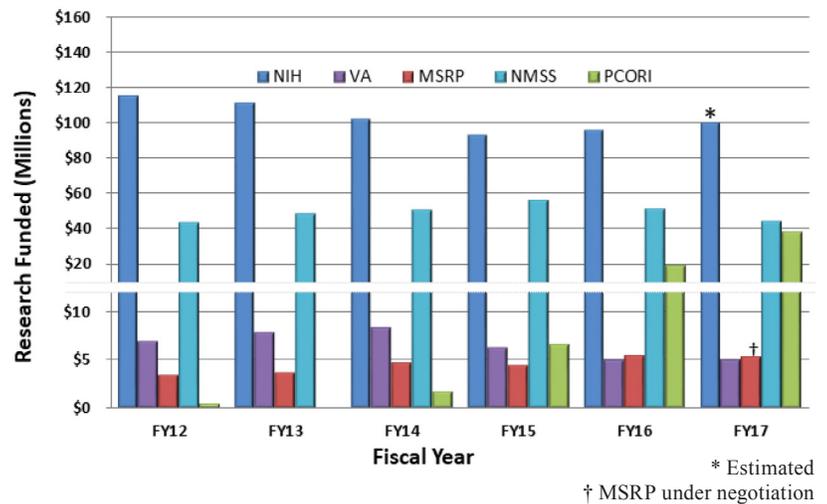
RESEARCH AND FUNDING ENVIRONMENT

FUNDING LANDSCAPE

In addition to MSRP, MS researchers may receive funding from other federal agencies such as the NIH and VA, as well as other non-federal agencies, including the National Multiple Sclerosis Society (NMSS) and the Patient-Centered Outcomes Research Institute (PCORI). Figure 4 shows investment in MS research from these organizations during FY12-FY17.

In order for MSRP to maximize its impact on MS research and patient care, the program coordinates with other organizations to identify research gaps, eliminate redundancy, maximize complementarity, and leverage their efforts. To assist with this objective, NIH and NMSS representatives serve on the MSRP Programmatic Panel.

Figure 4. Federal and Non-Federal Funding Landscape, FY12-FY17



* Estimated
† MSRP under negotiation

STATE OF THE SCIENCE

The MSRP monitors ongoing transformational research efforts in both MS and biomedical research in general, as well as evolving technologies that could alter the scientific landscape and cause the MSRP to reconsider and adjust the program’s strategic direction, goals, and priorities. These areas will be reviewed at future MSRP Vision Setting meetings to determine whether strategic adjustments are needed.

Ongoing transformational research efforts include: (1) clinical trials, registries, and imaging datasets; (2) genome-wide association studies and other large “omics” studies; (3) lifestyle research such as diet studies; (4) microbiome/gut-brain connection; (5) connectome studies investigating how parts of the brain are connected; (6) integration of patient care with clinical research; (7) bridging systems connecting genetic data to health outcomes; (8) prevention studies; (9) the relationship between neurodegeneration and inflammation; (10) commonality between MS and other neurological diseases; (11) repurposing medications, including generics; (12) libraries of diverse compounds with potential therapeutic effects; and (13) tools for improving clinical management and quality of care.

Evolving technologies that currently provide or could provide significant new tools to the MSRP research community and offer new avenues of research to address important questions include: (1) imaging technologies; (2) stem cell approaches; (3) single-stranded RNA; (4) whole genome sequencing methods; (5) machine learning/artificial intelligence; (6) telehealth and wearable technology; (7) high-throughput screening for drug identification; and (8) Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)-associated genome editing systems.

STRATEGIC DIRECTION

Taking into account the state of MS research, funding by other federal and non-federal agencies and the needs of the scientific and consumer community, the MSRP will continue efforts to prevent, cure, reverse, or slow the progression, and lessen the personal and societal impact of MS, with the ultimate goal to benefit Service members, Veterans, and the general public.

STRATEGIC GOALS

To address the Strategic Direction, MSRP identified the following four strategic goals, with specific scientific priorities identified for near- (1-3 years), medium- (3-5 years) and long-term (more than 5 years) goals:

1. Understand, measure, and treat relapsing and progressive aspects of MS; disease measurements will include clinical outcomes, patient-reported outcomes, and imaging and non-imaging biomarkers (including measures associated with the prodromal phase) *(medium term)*
 - Scientific priority: Correlates of disease activity and progression in MS *(near term)*
2. Identify strategies for neuroprotection, repair and restoration of function, and ultimately improving symptoms and quality of life *(medium term)*
 - Scientific priority: Obstacles to remyelination and/or obstacles to axonal protection in MS *(near term)*



3. Elucidate the cause and pathophysiology of MS symptoms that have a high impact on quality of life and develop treatment strategies (*medium term*)
 - Scientific priority: Biology and measurements of MS symptoms (*near term*)
4. Identify the role of various risk factors (genetics, environment, race and ancestry, age, comorbidities, risk behaviors, etc.) in MS etiology and disease course (*medium to long term*)
 - Scientific priority: Resources are not currently available to support this goal

INVESTMENT STRATEGY

To achieve its strategic goals, over the next 5 years, the MSRP will solicit research by providing funding for the following:

- Explore new ideas and untested concepts based on sound scientific rationale to generate preliminary data that will form the foundation of more robust hypothesis-driven research initiatives.
 - Exploration – Hypothesis Development Award
- Conduct preclinical and clinical laboratory research that is based on sound preliminary data and rigorous scientific methodology and has the potential to make significant contributions to MS research and patient care. Although preclinical and clinical laboratory research may take years to reach the patient, investments in such research are vital in forming the basis of ideas that have translational potential toward clinical interventions.
 - Investigator-Initiated Research Award

This investment strategy will be re-evaluated and updated as necessary during the program's annual Vision Setting meeting.

MEASURING PROGRESS

Metrics set measurable outcomes over the next 1- to 5-years by which progress toward the strategic goals can be gauged. The MSRP will measure its success in the short term based on successful investments in areas that are important to the strategic direction. Longer-term success will be evaluated based on contributions to the scientific community and follow-on research linked to MSRP-funded projects. Based on identified outcomes, MSRP may adjust the program's goals and priorities.

SHORT-TERM OUTCOMES (1-3 YEARS)

- Investment in research (amount and number of projects funded) leading to understanding, measuring, and treating relapsing and progressive aspects of MS
- Investment in research leading to strategies for neuroprotection, repair and restoration of function, and ultimately improving symptoms and quality of life
- Investment in research leading to understanding the cause and measurement of the MS symptoms that have a high impact on quality of life and development of treatment strategies
- Investment in projects testing novel hypotheses/new concepts

MEDIUM-TERM OUTCOMES (3-5 YEARS)

- Contributions to the scientific community (presentations, publications, patents, etc.)
- Follow up federal and non-federal funding to expand research based on knowledge gained by MSRP-funded projects
- Number of ongoing pilot clinical trials completed by 2023

REFERENCES

1. *Evaluation of the Congressionally Directed Medical Research Programs Review Process, a Report of the National Academies of Sciences, Engineering, and Medicine*. 2016. The National Academies Press, Washington, DC. (<http://nationalacademies.org/hmd/reports/2016/cdmrp.aspx>).