

Accelerating Functional Recovery of Multiple Sclerosis

The mission of the National Multiple Sclerosis Society is to cure multiple sclerosis (MS) while empowering individuals affected by MS to live their best lives. To achieve this mission, the Society has developed the Pathways to Cures Research Roadmap (<https://journals.sagepub.com/doi/full/10.1177/13524585221075990>). The Roadmap was developed in consultation with global scientific experts and people affected by MS and outlines a vision of the most promising research that will ultimately lead to cures for MS. **A high priority objective of the Roadmap is to restore lost function by reversing damage and symptoms. This request for applications (RFA) is designed to solicit research that advances this specific objective.**

Background

MS is an immune-mediated disease of the central nervous system (CNS) that often leads to significant progressive long-term disability. Accumulating evidence suggests that localized acute inflammation, as well as more widespread, chronic, compartmentalized inflammation and neurodegeneration, are driving disability progression. In addition, the gradual failure of compensatory mechanisms such as neuroplasticity and remyelination associated with aging is also likely playing an important role.

We now know that the CNS has substantial potential for structural and functional adaptations after injury and recovery of function has been demonstrated. The development of therapeutic strategies that promote functional recovery in MS is a major goal of the Pathways to Cures research roadmap. Recent scientific and methodological advances have improved our understanding of the central nervous systems ability to recover from damage and this knowledge is revealing new targets for both pharmacological, non-pharmacological (e.g., rehabilitation) interventions and even combination approaches with the potential to restore lost function in people with MS.

Rehabilitation aims to optimize physical and cognitive function and overall quality of life, incorporating preventive, restorative, compensatory, and maintenance approaches. Recent studies have revealed that rehabilitation improves everyday activities, function, and quality of life for people with MS. In some cases, this functional recovery is accompanied by demonstrable CNS reorganization/evidence for neuroplasticity/compensation. This points to a significant opportunity to explore the potential of rehabilitation therapies to address pathologic as well as symptomatic recovery and the idea of combining rehabilitation with remyelination/neurorestorative compounds.

Exercise therapy has a very limited risk profile but can have profound symptomatic benefits for people with MS. Even in the early stages before functional limitations exist, there is emerging evidence of the disease-modifying benefits of exercise. In animal models exercise has been shown to influence remyelination, neuroinflammation growth factor levels, and blood-brain barrier integrity. Animal studies have reported that exercise following toxin-induced demyelination in mice enhanced oligodendrogenesis, the rate of remyelination, and the proportion of re-myelinated axons. Further, exercise in parallel with the remyelinating medication clemastine produced near-complete remyelination of lesions.

Diet as a possible disease-modifying intervention for MS is also being explored. Although there is no specific diet for MS, there is evidence that many dietary components modulate mechanisms such as immune and mitochondrial function, oxidative stress, and gut microbiota and are hypothesized to influence disease progression.

The importance of cognitive reserve and the positive impact of cognitive rehabilitation therapy has been reported. Cognitive therapy can be delivered remotely using innovative brain stimulation technologies like transcranial direct current stimulation that elicit changes in brain activity and brain connectivity in people with MS, resulting in improvements in symptoms.

The broad variety of symptoms in MS including depression, fatigue, pain, and walking dysfunction impact each person to a different extent, this heterogeneity makes them difficult to study. Expanding our understanding of the impact of demographic features (e.g., age, race, ethnicity) on symptoms offers potential opportunities for improving personalized treatment.

Finally, outcome measures are an important consideration for designing clinical trials and will require testing and validation so that the effectiveness of non-pharmacologic therapies can be measured and reported with confidence. A high-priority need is for sensitive and specific outcome measures that detect a clinical change in a shorter period of time. For example, the advances in real-time data from wearable technology and other applications offer opportunities to develop outcomes that can detect and quantify a clinically meaningful change.

Overall, these and other non-pharmacological approaches for slowing, stopping, or even reversing neurodegeneration and disability progression offer the potential for functional recovery. **This RFA is designed to move past the separation of foundational science and rehabilitation science and push for collaborative research that accelerates both the acquisition of knowledge and application of this knowledge into approaches that benefit people with MS.** Additional research is needed to better understand the mechanisms leading to functional recovery to optimize effective non-pharmacologic intervention options for people with MS.

Purpose of this RFA

This concept supports innovative and collaborative studies that accelerate the acquisition of mechanistic knowledge and application of this knowledge to improve functional recovery for people with MS. This will be accomplished through a multi-year research grant-style mechanism, offering up to 3 years of funding for up to \$660,000 (direct costs).

The focus of this initiative is two-fold:

- Addressing mechanistic knowledge gaps to enhance function in MS
- Developing novel non-pharmacological and/or combination approaches that draw on our knowledge of remyelination, neural protection, and plasticity

Areas of specific interest may include but are not limited to:

- Mechanistic study of remyelination and/or neural repair associated with rehabilitation and other non-pharmacological approaches to restore function
- Collaborative approaches that combine mechanistic studies with rehabilitation methods and other non-pharmacological strategies
- Clinical studies can be complemented by pre-clinical animal work
- Interaction among and between demographic features (e.g., age, race, ethnicity) and common MS symptoms such as fatigue, depression, pain, cognition, and walking
- Identification of timing, dosing, setting, and specificity of exercise to restore function
- Evaluation of outcomes (e.g., behavioral, physiologic, imaging) that show evidence to detect a meaningful change in function
- Synergistic studies of pharmacologic and non-pharmacologic therapies
- Use of technology for enhancing treatment effectiveness and for understanding the mechanisms of treatment effects
- Identification of biomarkers and tools that establish direct relationships between physiologic findings and meaningful recovery of function

Areas NOT supported by this RFA include:

- Testing of pharmacologic treatments alone or in combination with other pharmacologic treatments
- Mechanistic studies that do not focus on functional recovery

Qualified Institutions:

This RFA is open to investigators at not-for-profit research institutions. Collaborations with commercial organizations are allowed

Funding: Up to \$660,000 USD direct costs for up to three years of support will be provided and must be justified based on the scientific work plan

Submission guidelines and process: Important dates:

- Pre-applications will be accepted beginning: **11/22/2022**
- Final date for acceptance of pre-applications: **1/18/2023**
- Final date for receipt of full applications: **1/25/2023**

A brief pre-application is required to determine if a proposal is aligned with the objectives of the RFA.

Potential applicants are strongly encouraged to consult with Society scientific staff prior to submitting a proposal (see contact information below). Applications are to be submitted through the National MS Society's online grant submission portal - MSGrants. All proposal information, including instructions for accessing MSGrants, can be found at

<https://nms2cdn.azureedge.net/cmssite/nationalmssociety/media/msnationalfiles/research/applicationinstructionsresearchgrants.pdf>. Upon review of pre-applications by staff, applicants proposing work that is aligned with the RFA objectives will be invited to submit full applications.

The reviewers will evaluate proposals based on the following criteria:

- **Rationale:** Are the hypotheses based on published literature and/or sufficient preliminary data? Would testing the hypotheses lead to a significant advance in knowledge relevant to Pathways to Cures?
- **Relevance:** How well does the proposal align with the objectives of the RFA?
- **Preliminary Data:** Has the applicant provided sufficient preliminary data to demonstrate they have the skills and expertise to carry-out the proposed studies? Does the data provide reasonable preliminary support for the project?
- **Research Team:** Are the lead investigator and collaborators qualified and well-suited to carry out the proposed research?
- **Scientific Plan:** Is the research plan sufficiently developed and appropriate to the project? Are the specific aims clearly defined? Has the investigator considered alternative outcomes and the impact on the plan? Is the analysis plan and statistical methodology appropriate for the project?
- **Environment:** Is the research environment appropriate and likely to contribute to the success of the proposed research? Does the environment foster collaborative arrangements that may support the proposed research activities? Is the research environment compliant with appropriate rules and regulations for study conduct?
- **Budget:** Is the proposed budget reasonable and justified relative to the proposed research?
- **Plain Language Description.** Applicants must provide a plain language description of the proposed project, responding to the following questions: What is the question and hypothesis(es) related to MS that you are addressing with this project? What are the aims of this project, and how do they address the question related to MS? Describe your experimental approach. For studies that include people, please describe what is involved for participants in this study. How might the results of this study potentially make life better for people affected by MS?

Applicants will be notified of results at the conclusion of the review process. We anticipate communicating the outcomes by

Applicants are encouraged to contact Society scientific staff for clarification of any issues or questions regarding this RFA.

Kathy Zackowski, PhD, OTR	Associate Vice President, Research	Kathleen.Zackowski@nmss.org
Anna Lampe, PhD	Director, Research	Anna.Lampe@nmss.org