National Multiple Sclerosis Society

2024 REQUEST FOR APPLICATIONS

Generating Knowledge and Tools to Promote Remyelination and Neuroprotection in 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. 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. This request for applications (RFA) is designed to solicit research that advances this objective.**

Background: The approval of more than 20 immunomodulatory disease-modifying therapies (DMTs) has dramatically improved the quality of life for people with relapsing forms of MS. For those who have achieved infrequent relapses and/or disease stabilization, therapies to promote remyelination are a high priority. Such therapies would likely accelerate relapse recovery and slow down the processes that lead to disability accumulation. While several agents to promote remyelination have been evaluated in clinical trials, none has been successful in demonstrating objective clinical benefits. The remyelination of demyelinated axons occurs to some extent naturally, although with less efficiency as the disease progresses, and remyelination protects the axon, supports metabolism, and improves axonal function. Additional approaches to augment or promote this process in an MS environment are needed. Neuroprotective agents that extend the viability of damaged neurons hold promise as adjunct treatment to promote repair.

While considerable progress has been made studying remyelination in preclinical models, clinical translation of potential remyelinating agents has not yet been successful. Preclinical studies of remyelinating agents are often done using rodent toxin models such as the cuprizone and lysolecithin models which allow for more controlled interrogation of remyelination. These models have known limitations including the young age of the animals, the lack of the autoimmune environment found in MS, and the observation that remyelination is robust in these models without treatment, which is not the case in MS. New or modified animal models that more accurately model aspects of the MS remyelinating environment would be valuable for the field.

Disease heterogeneity also hinders translation, as studies with post-mortem MS brain tissue have shown that the extent of endogenous remyelination in lesions can vary between individuals and even between different lesions in the same individual. The extent of remyelination also differs based on lesion type. There is much we still do not understand about endogenous remyelination in MS, including why it diminishes with age and over the disease course and which pathways may be most amenable to therapeutic intervention in an MS environment that may include ongoing inflammatory activity. Approaches that have been explored in clinical studies include promoting the differentiation of oligodendrocyte precursor cells (OPCs) in the lesion to myelinating oligodendrocytes and blocking interactions with environmental inhibitory factors. Evidence also suggests a role for neuronal activity in

promoting remyelination. Engaging multiple approaches or targets may be necessary for optimal remyelination.

One challenge for the development of remyelination therapies is a need for validated and reliable biomarkers to evaluate efficacy in the clinic. Recent trials of potential remyelinating agents have relied on improvements in visual evoked potential (VEP) latency in individuals with optic neuritis as a functional measure indicative of remyelination. Several magnetic resonance imaging (MRI)-based approaches to measure the state of myelination have been investigated, however, none has yet emerged as an accepted standard. Positron emission tomography (PET)-based approaches to measure myelin directly offer a potential complementary approach. A gap in biomarker efforts is the lack of approaches to measure the state of grey matter/cortical myelination.

Damage to the myelin sheath not only impacts signal propagation and metabolism in the affected axon, but also leaves the axon vulnerable to further damage. Studies suggest that under chronic demyelinating conditions there is a time window beyond which accumulated axonal damage is beyond repair. Interventions that stabilize or protect neurons or damaged oligodendrocytes would be important adjunct treatments for remyelination strategies.

Studies of neurodegeneration in model systems and in post-mortem MS tissue suggest that changes in mitochondrial function, trafficking, and biogenesis represent an early sign of neuroinflammation and demyelination. Mitochondria accumulate in damaged axons, perhaps as a compensatory mechanism to address energetic imbalance. Studies of demyelinated axons have shown evidence of the loss of synaptic proteins. In addition, demyelination is thought to trigger a complement-mediated microglial response that results in synaptic loss. Neurodegenerative processes in MS are relatively understudied. There may be opportunities to learn from mechanisms under evaluation in other neurodegenerative diseases. While immunomodulatory therapies have slowed neurodegeneration, presumably as a secondary effect of reducing inflammation, to date no therapeutic approaches directly targeting neuroprotection have shown objective clinical benefits. An improved understanding of potential interventions that stabilize axons and synapses is needed to support remyelination.

Neurodegeneration is most often evaluated using brain MRI atrophy measures. While atrophy measures have been useful in clinical trials, the measurement of atrophy has typically been done over the course of 2 years. Methods that could detect neurodegenerative changes more quickly would be valuable. Significant progress has been made in the study of fluid biomarkers such as serum neurofilament light chain (sNfL) and glial fibrillary acidic protein (GFAP), proteins found in neurons and astrocytes respectively. Correlations have been observed with sNfL for acute disease activity and prediction of subsequent MRI lesion activity, brain volume loss, relapse rate, and worsening of disability. GFAP, while still emerging as a biomarker, may hold potential as a biomarker for progression. Optical coherence tomography (OCT) imaging of the retina allows for the resolution of cellular layers and has potential for monitoring neurodegeneration. Retinal thinning has been correlated with clinical disability and brain atrophy in MS independent of optic neuritis.

Purpose of this RFA: This funding concept supports research that addresses gaps in our knowledge of the underlying biology of CNS remyelination in MS, the factors or processes that modulate this process, and methods to measure remyelination. Additionally, research into neuroprotective mechanisms with the potential to prolong neuronal viability for remyelination is encouraged. The supported research is intended to lay the foundation for the next generation of therapeutic approaches.

In addition, the concept supports the development or refinement of tools needed to support preclinical and clinical studies of remyelination and neuroprotection in MS, including in vitro and animal models that more closely reflect MS pathophysiology and clinical biomarkers with utility for measuring CNS myelination and neuroprotection. Applications proposing the testing of new or established biomarkers must include relevant components of analytical method validation to ensure that a test, tool, or instrument is adequate for its proposed context of use.

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

- Studies of mechanisms underlying endogenous remyelination in MS.
- Investigations into the basis of the heterogeneity of endogenous remyelination observed across lesion types and between individuals living with MS.
- Studies of factors that modulate remyelination in MS.
- Studies of mechanisms to provide neuroprotection or oligodendrocyte protection.
- *In vivo* and *in vitro* model systems that more closely mimic MS pathology with utility to study interventions supporting remyelination.
- Clinically translatable biomarkers for the measurement of remyelination or neuroprotection.
- Preclinical proof of concept studies for potential therapeutic targets to promote remyelination or neuroprotection. Studies could involve small molecule drugs, cell-based strategies, biologics, genetic models, or other suitable approaches.

Areas not supported by this RFA include:

- Studies addressing developmental myelination.
- Investigation of neurodegenerative mechanisms without a therapeutic focus.
- Studies of the adaptive immune system unrelated to remyelination.
- Studies of anti-inflammatory mechanisms that indirectly create an environment conducive to repair.

Submission guidelines and process:

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

Funding: Up to $1,000,000 USD total costs (including indirect costs where applicable) for up to 3 years of support will be provided and must be justified based on the scientific work plan. Applicants with proposals of high potential impact that require budgets of over $1,000,000 USD and/or more than 3 years of support should contact a program officer to determine if it can be considered under this mechanism.

Preliminary Data: Applicants are expected to provide preliminary data in support of their hypothesis and demonstrating the feasibility of the proposed studies.

Important dates:

- Pre-applications will be accepted beginning: **October 5, 2023**
- Final date for acceptance of pre-applications: **January 3, 2024 | 5:00 pm Eastern Time**
- Final date for receipt of full applications: **January 10, 2024 | 5:00 pm Eastern Time**

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 online. Upon review of pre-applications by staff, applicants proposing work 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 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?
- **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?

Applicants will be notified of results after evaluation by Scientific and Community Review committees in the late summer of 2024 and grants are expected to start October 1, 2024.

- **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? The Plain Language Description will be used by volunteer community reviewers who will provide their expertise based on their lived experience with MS and that feedback will be used to as part of prioritizing scientifically meritorious applications for funding consideration.

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

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