Therapeutic Development Opportunities Addressing Nervous System Repair 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. The Pathways to Cures Roadmap will inspire the alignment of global resources on the most pressing questions in MS research and accelerate scientific breakthroughs that lead to cures for everyone living with MS.

This RFA invites applications to establish research partnerships with the Society's commercial development program, Fast Forward, LLC, to accelerate and support development of therapeutic strategies and biomarkers relevant to the Roadmap priority of Nervous System Repair in MS. This RFA is open to applicants from for-profit commercial organizations and not-for-profit research institutions worldwide (see Mechanisms of Support section for additional important details).

Background: Current disease modifying therapies (DMTs) for MS are thought to work by modulating aspects of the adaptive immune system. They have been shown to be effective in limiting the occurrence of relapses and in some cases delay disability worsening, however, these therapies have very limited capacity to enhance or restore lost function. To this end, there is an urgent need for therapies that promote repair and regeneration. The MS disease process results in CNS demyelination and neuronal damage that ultimately manifests in lost function. The brain can repair myelin, especially early in the course of MS, but the mechanisms underlying the eventual failure of repair are not fully understood.

In endogenous remyelination, oligodendrocyte precursor cells (OPCs) migrate to the site of injury and differentiate into mature oligodendrocytes, which myelinate axons. Some research suggests that surviving adult oligodendrocytes can also participate in myelin repair. Investigators have shown that MS lesions contain OPCs, however as the disease progresses, remyelination is less efficient. One strategy to improve remyelination has been to develop therapeutic candidates that promote differentiation of OPCs. Clemastine fumarate was shown to promote remyelination in vitro and in animal models. A phase II clinical trial (ReBuild) demonstrated a modest benefit for Clemastine fumarate in people with MS with chronic demyelinating optic neuropathy. A phase II clinical trial in acute optic neuritis is underway (ReCover).

A complementary approach to directly promoting differentiation of OPCs has been to make the lesion environment more permissive for repair. Investigators have shown that demyelination produces inhibitory factors (myelin debris, cytokines, inflammatory mediators). Myelin debris inhibits oligodendrocyte remyelination at least in part through an interaction with a signaling complex containing Lingo-1. Anti-Lingo-1 antibodies promote remyelination *in vitro* and in animal models. The anti-Lingo-1 therapeutic candidate Opicinumab (BIIB033) was evaluated in three phase II studies. While

the clinical trial results did not support further development, these trials were among the first looking at a potential remyelination promoting agent.

An alternative approach to blocking interactions with inhibitory factors is modulating the innate immune system. Astrocytes and microglia have been shown to manifest a diverse range of phenotypes that include both permissive and destructive effects on repair, thereby suggesting that phenotype-selective targeting may be viable. For example, microglia are thought to play a role in both creating myelin debris and in the clearing of myelin debris. Potentiating the removal of inhibitory factors represents a potential therapeutic approach. Studies suggest that the lesion environment is also less permissive for remyelination with aging. This suggests the presence of aging related factors that could be modulated.

Remyelination requires the preservation of axons. In MS there is synaptic loss and damage to demyelinated axons including transection. Demyelinated axons suffer metabolic stress. Mechanisms to preserve axons and provide a substrate for remyelination are of interest. For example, the voltage gated sodium channel blocker Phenytoin was evaluated in a phase II study in optic neuritis. The study showed potential evidence of neuroprotection and provided data to better understand the importance of the timing neuroprotective agents relative to demyelinating events.

In addition to small molecule and biologic therapies, cellular therapies are also being studied. Mesenchymal stem cell infusions have been the subject of several clinical trials, mostly smaller studies at individual institutions. There have been some reports of positive immunomodulatory effects. More recently neural stem cells have been reported to both enhance repair and modulate inflammation. Clinical studies of neural stem cells administered intrathecally are underway. While these cell therapies are transient and will require re-administration, there is also active research on stem cell approaches to deliver cells that will integrate and assume the function of damaged or lost cells.

As a new therapeutic direction there is continuing interest in clinical endpoints to evaluate remyelination. Studies of remyelination agents in optic neuritis have employed optic nerve visual evoked potentials as an indirect measure of myelin integrity. Advanced MRI imaging techniques such as magnetization transfer ratios and myelin water fraction are in use in clinical trials. PET ligands to monitor remyelination are also under development. Projects with a commercial orientation to develop and/or validate methods or tools to monitor remyelination will also be considered within this RFA.

As illustrated by the brief description above, there are many strategies under active exploration to promote repair. There is a growing sense that optimal remyelination and repair may require addressing multiple pathways.

This RFP is intended to catalyze therapeutic development efforts in the area of Nervous System Repair in MS. Further guidance on the types of work to be supported within proposals is provided below:

Examples of research and development to be supported by this RFA include, but are not limited to:

- Medicinal chemistry or biologic product development optimization
- Studies to measure target engagement or target-related pharmacodynamic effects, particularly those involving endpoints with clinical utility
- Proof of concept for sufficiently characterized compounds or biologics

- PK/ADMET studies
- IND-enabling studies such as GLP toxicology, compound scale-up, process method validation
- Studies to validate or optimize commercially viable endpoints to measure nervous system remyelination and/or repair in the clinical setting

Research areas NOT supported by this RFA:

- New target identification studies
- High-throughput screening and early hit characterization
- Drug repurposing efforts without a commercially appropriate intellectual property strategy

Mechanisms of support:
This RFA is open to for-profit commercial organizations and not-for-profit research institutions. Consistent with our goal to support research and development conducted with a high level of quality control typical of the pharmaceutical industry, applications from not-for-profit institutions will be considered if most of the work is conducted at reputable Contract Research Organizations with appropriate expertise or is conducted in such fashion in a suitable research environment with strict adherence to quality control measures. The project duration should be 1 to 2 years.

Funding: Up to $800,000 USD direct cost will be provided and must be justified based on the scientific and development work plan.

Submission guidelines and process: Important dates:

- Pre-applications will be accepted beginning **October 19, 2022**
- Final date for acceptance of pre-applications: **5 pm ET, January 4, 2023**
- Final date for receipt of completed full applications: **5 pm ET, January 11, 2023**

A brief pre-application is required to determine if a proposal is aligned with the objectives of the RFA. Inquiries with Fast Forward staff are strongly encouraged (see contact information below). Applications are to be submitted through the National MS Society's online grant submission portal - MSGrants. All application information, including instructions for accessing MSGrants, can be found at http://www.nationalmssociety.org/For-Professionals/Researchers/Society-Funding/Commercial-Research-Funding. Upon review of pre-applications by staff, only those applicants proposing work aligned with the RFA objectives will be invited to submit full applications for review. Applications will undergo evaluation by Fast Forward's Scientific and Business Advisory Committee (SBAC). Selected competitive applicants will be expected to present and answer questions at a teleconference with members of the Fast Forward SBAC.

Proposals will be reviewed based on the following criteria:

A. Scientific Considerations:

- **Rationale**: Does the applicant address an important aspect of the RFA?

- **Innovation:** Does the project address an innovative hypothesis, novel target, or critical barrier to progress in the field? Does the project develop or employ novel concepts, approaches, methodologies, tools, or technologies for this area?
- **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? Are milestones and go/no go decision points articulated? Are the milestones and timeline realistic?
- **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?

B. Commercial Considerations:

- **Commercial Feasibility**: Does the proposal define a potential path to the marketplace? What are key milestones or barriers to achieve commercialization?
- **Development Potential**: Is there a development path that enables advancement through preclinical and/or clinical development?
- **Intellectual Property**: Has the applicant secured intellectual property for the technology? If not, is this in process?
- **Funding by Third Parties**: Has the proposed research program been evaluated by other entities that have provided external support?

Applicants will be notified of the review outcome in Q2 of 2023. Awards will be provided pursuant to a Sponsored Research Agreement covering details of milestone-based project support and terms of revenue sharing.

Inquiries:

Applicants are encouraged to contact Fast Forward staff for clarification of any issues or questions regarding this invitation.

Mark Allegretta PhD	Vice President, Research	mark.allegretta@nmss.org 212-476-0459
Walter Kostich PhD	Senior Director, Commercial Research	walter.kostich@nmss.org 212-476-0428