

## **Therapeutic Development Opportunities Addressing MS Progression and Progressive Forms of MS**

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](#). This 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.

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 specifically relevant to the Roadmap priority of addressing MS progression and progressive forms of 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:** Over the last thirty years more than twenty immunomodulatory therapies have been approved for the treatment of MS. These therapies have largely been directed at the adaptive immune system and have dramatically reduced relapses. However, most MS therapies have been ineffective when evaluated in progressive forms of MS and those that have been approved for progressive forms of MS still leave significant unmet need. Hence additional therapies more targeted at the pathophysiology of progressive forms of MS are sorely needed.

In addition, there has been recent recognition that many people living with relapsing-remitting MS that have achieved good radiographic and clinical relapse control are still accumulating disability over time in a process that has been termed Progression Independent of Relapse Activity (PIRA). While less is known about the underlying progressive processes underlying PIRA, it suggests that therapies that target progressive MS could have utility beyond the primary progressive and secondary progressive MS population. The emerging literature suggests the involvement of the innate immune system and compartmentalized inflammation as important drivers of progressive MS. Therapies that target these areas remain a major unmet need. Neuroprotective therapies that slow the neurodegenerative process are also of interest as adjunct therapies.

Pathological features of particular interest include slowly expanding lesions and leptomeningeal inflammation. Longitudinal MRI shows that slowly expanding or mixed active lesions expand out from an inactive or "burned out" core over the course of months or years. The leading edge of these lesions contains phagocytic microglia/macrophages. In the case of leptomeningeal inflammation, immune cell clusters can form within the leptomeningeal space lining the brain and spinal cord and these cells organize in a manner reminiscent of lymphoid follicles. Leptomeningeal inflammation is associated with subpial lesions and can result in extensive

cortical demyelination. Finally, evidence of diffuse extra-lesional inflammatory activity is also observed, for example activated microglia and microglial nodules in the white matter.

CNS-resident cells that play a role in the innate immune response, particularly microglia and astrocytes, have been of interest in the search for potential therapeutic targets for progressive MS. The range of phenotypes expressed by microglia and astrocytes are more complex than previously appreciated. Both cell types can produce a range of protective and destructive responses. Approaches that promote therapeutic phenotypes are of considerable interest.

An important adjunct strategy to targeting neuroinflammation is neuroprotective strategies. This involves directly protecting neurons from degeneration. Studies of neurodegeneration in model systems and in post-mortem MS tissue suggest changes in mitochondrial function, trafficking, and biogenesis represent an early sign of neuroinflammation and demyelination. 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. Promoting neuroprotection has the potential to prolong neuronal viability, preserve neuronal function, slow disability progression, and improve opportunities for endogenous remyelination.

The above descriptions are far from comprehensive and are not meant to be restrictive. This RFA is open to commercially viable therapeutic approaches to treat progressive MS and/or delay or prevent PIRA. Adjunct neuroprotective therapeutic approaches are also encouraged. Therapeutic modalities can include small molecules, biologics, and cellular therapies. 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:**

- Proof of concept studies using sufficiently characterized compounds or biologics.
- Studies to measure target engagement or target-related pharmacodynamic effects, particularly those involving endpoints with clinical utility.
- Medicinal chemistry or biologic product development optimization.
- PK/ADMET studies
- IND-enabling studies such as GLP toxicology, compound scale-up, process method validation

**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
- Targets exclusive to immune pathways in MS pathophysiology that are known to drive acute inflammatory responses in the relapsing forms/phases of MS.

## **Submission Guidelines and Process:**

### **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:**

Direct costs of up to **\$800,000 USD** will be provided and must be justified based on the scientific and development work plan.

### **Important dates:**

- Pre-applications will be accepted beginning: **November 16, 2023**
- Final date for acceptance of pre-applications: **January 24, 2024 | 5:00 pm Eastern Time**
- Final date for receipt of full applications: **January 31, 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.**

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:

### **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? 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?

**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 2024. 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.

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