National Multiple Sclerosis Society

2022 REQUEST FOR APPLICATIONS

Generating Knowledge and Tools to Address Compartmentalized Inflammation 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 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 address compartmentalized inflammation in MS. This request for applications (RFA) is designed to solicit research to advance this objective.

Background

Current MS disease modifying therapies (DMTs) are largely directed at peripheral (adaptive) immune responses and have been effective in dramatically reducing clinical and radiological relapses. Unfortunately, these therapies may delay, but do not prevent progression and disability accrual. Recently there has been a growing appreciation of the potential role of chronic compartmentalized inflammation in driving progression. Compartmentalized inflammation occurs behind a largely intact blood-brain barrier (BBB) and is thought to contribute to processes underlying progressive forms of MS.

Our understanding of compartmentalized inflammation has improved significantly over the last few years. In the early stages of MS, the disease is dominated by perivenular inflammatory white matter lesions of the brain and spinal cord. These lesions can be observed with magnetic resonance imaging (MRI) and if active may show gadolinium contrast enhancement due to BBB disruption. The lesions undergo some degree of endogenous repair over the course of weeks or months.

New inflammatory white matter lesions become less frequent with increasing age and progression. About twenty percent of the white matter lesions are thought to evolve into “mixed active/inactive” or “smoldering” lesions. Longitudinal MRI shows these lesions slowly expand out from an inactive or “burned out” core over the course of months or years. Unlike the active inflammatory lesions, these lesions are found inside of a more intact BBB. The leading edge of these lesions contains phagocytic microglia and infiltrating macrophages which take up iron and are visualized using susceptibility-based MRI sequences. They are termed paramagnetic rim lesions (PRLs).

Another example of compartmentalized inflammation is leptomeningeal inflammation. Immune cell clusters can form within the leptomeningeal space lining the brain and spinal cord and these cells sometimes organize in a manner reminiscent of lymphoid follicles. Leptomeningeal inflammation is associated with subpial lesions and can result in extensive cortical demyelination. Leptomeningeal lymphoid follicles are found in about 40% of people with progressive MS and are associated with more rapid progression. Finally, extra-lesional inflammatory activity is also observed, for example diffuse activated microglia and microglial nodules in the white matter.

Despite recent progress, there is an urgent need to better understand the biological mechanisms underlying compartmentalized inflammation. A mechanistic understanding is critical in identifying targets for new therapeutics. Focus has increased on potential contributions of glial cells, specifically astrocytes and microglia, to compartmentalized inflammation. A major challenge in MS pathogenesis is delineating the mechanism of subpial demyelination and lesion expansion. Since peripheral immune cell

infiltrates are not a feature of subpial lesions, cortical microglia likely play a role. More work is needed to determine the role meningeal immune cells play in driving subpial demyelination.

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, based on transcriptional profiles. It was recently reported that at the edge of smoldering lesions the astrocytes and microglia adopt a neurodegenerative profile that is shared with other neurodegenerative diseases.

In addition, the field needs in vivo and in vitro models to study compartmentalized inflammation preclinically and models that can help demonstrate proof of biology for pathways thought to play a role in progression. Biomarkers are needed that will allow tracking of compartmentalized inflammation for research and ultimately for disease management. These could come from a host of imaging approaches (MRI based, PET etc.) or through assays of body fluids (blood, CSF, etc.).

Purpose of this RFA

This initiative will support projects generating fundamental knowledge, technologies, and model systems to lay the groundwork for future treatments for MS that target compartmentalized inflammation.

- Addressing knowledge gaps around the formation and maintenance of compartmentalized inflammation
- Developing the tools researchers need to model compartmentalized inflammation in a preclinical setting and to validate targets for translation into therapeutic approaches

Areas of high interest include:

- Pathophysiology of compartmentalized inflammation including:
    - Processes driving the formation and maintenance of compartmentalized inflammation
    - Role and regulation of innate and adaptive immune cell populations
    - The role of glial cell populations
    - Effector mechanisms that result in cell and tissue loss in this setting
    - Potential contribution of race/ethnicity to compartmentalized inflammation
- Model systems (in vitro and in vivo) that capture aspects of compartmentalized inflammation based on disease pathology
- Biomarkers for monitoring compartmentalized inflammation with potential translation to the clinic, including imaging, blood and CSF based approaches
- Proof of concept studies testing new potential therapeutic pathways or targets

Areas not supported include:

- Studies focused on prevention of acute inflammatory lesion formation
- Proposals that require building new long-term resources: patient cohorts, repositories, etc.

Qualified Institutions:

This RFA is open to not-for-profit research institutions worldwide.

Funding: A total of up to $600,000 USD direct cost for up to three years of support will be provided and must be justified based on the scientific and development work plan.

Submission guidelines and process: Important dates:

- Pre-application Deadline: 5:00 pm Eastern Time, **March 23, 2022**
- Full application Deadline: 5:00 pm Eastern Time, **March 30, 2022**

Applicants will be notified in Fall 2022 of results after evaluation by Scientific and Community Review committees. Funded grants will begin on or about **October 1, 2022.**

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 this link**. Upon review of pre-applications by staff, applicants proposing work that is aligned with the RFA objectives will be invited to submit full applications.

Reviewers will evaluate proposals based on the following criteria:

- **Rationale**: Are the hypotheses based on valid literature 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 Summary**. The Society's review process now includes a Community Review of MS Research Committee. This committee includes people affected by MS, experts because of their experience with MS. This Plain Language Description will serve as the basis for Community Reviewers to assess and score how well the proposal aligns with MS community priorities. It is an important part of the overall application, and we encourage you to **click here for examples of** top-notch plain language science writing and other resources.

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

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