

Elucidating the Role of Viruses in Initiating and Driving Pathologies in Multiple Sclerosis

Objective:

This concept proposes to use a Request for Applications funding mechanism to solicit pilot research proposals that address [Pathways to Cures](#) by exploring the interplay between viruses and Multiple Sclerosis (MS). Of particular interest is defining mechanisms through which viruses may contribute to the initiation or course of disease pathologies in people with MS. The pilot mechanism is intended to support the generation of preliminary data, feasibility studies, and tool development to position the recipient to successfully apply for future longer-term funding of novel and impactful research in this area. Full studies that can be completed within the pilot budget and timeframe are also welcome.

Background:

MS is a complex disease with genetic, environmental, and immunological factors contributing to the disease etiology. It remains unclear what precise role viruses such as Epstein-Barr virus (EBV), human herpesvirus 6 (HHV-6), varicella-zoster virus (VZV), and human endogenous retroviruses (HERVs) may play in MS development and progression. However, recent studies have refocused attention on the roles of viruses in this disease.

For many years, EBV has been a leading candidate among the suspected causative agents for MS. EBV is a human herpesvirus that infects approximately 95% of adults and persists after infection in latent form, primarily in B cells, throughout the life of the host. A causal role of EBV is supported by the increased MS risk associated with infectious mononucleosis or elevated serum antibody titers against EBV nuclear antigens. Additionally, some pathological studies have shown the presence of EBV in MS demyelinated lesions – though other studies have failed to detect the virus. The recent work of the Harvard School of Public Health with a large US Military cohort – showing near ubiquitous EBV seropositivity in a cohort of 801 subjects who developed MS – provides new and compelling evidence that EBV infection is necessary for the development of MS ([Bjornevik et al, 2022](#)).

However, the mechanism (or mechanisms) linking EBV infection to the development of MS remains unclear. One possible link is through molecular mimicry between EBV antigens and self-antigens in the central nervous system (CNS). Antibodies against certain EBV nuclear antigens (such as EBNA-1) have been identified in people with MS. Furthermore, a recent study showed cross-reactivity between antibodies that bind EBNA-1 and GlialCAM, a molecule expressed in the CNS ([Lanz et al, 2022](#)). Taken together, these data indicate a possible role for EBV in MS initiation through molecular mimicry.

In addition, B cells infected with EBV have been identified in the CNS of people with MS ([Moreno et al, 2018](#)). This direct link between B cells (known to play a critical role in MS disease pathology) and EBV points to possible cell-specific effects of latent or active EBV infection on B cell activity in an autoimmune, neuroinflammatory environment. In fact, some hypothesize the efficacy of B cell-depleting therapies may be in part due to the elimination of EBV-infected B cells, though direct evidence of this remains elusive.

Finally, there is evidence that EBV infection, aside from merely triggering disease onset, could also play a role in ongoing disease pathology. Studies have found increased EBV-related immune responses (EBV-specific T cells and anti-EBV antibodies) during elevated MS disease activity ([Pender et al, 2017](#); [Lunemann et al, 2010](#)). Additionally, there is speculation that EBV could drive damage within the CNS by eliciting a broad, antiviral response ([Magliozzi et al, 2013](#)). The importance of EBV in MS is emphasized by several recent high-impact research studies and clinical trials; including a Phase 2 trial (EMBOLD study; ClinicalTrials.gov Identifier: [NCT03283826](#)) evaluating the efficacy and safety of a cell-based, allogeneic EBV therapy (Atara Bioscience, ATA188) in progressive forms of MS.

Apart from EBV, several other viruses have been implicated in the development and progression of MS pathology. For example, HERVs have long been implicated in the neuroinflammation of MS. Additionally, viruses like VZV and HHV-6 have shown to be correlated with MS onset and progression ([Manouchehrinia et al, 2017](#); [Pormohammad et al, 2018](#)) – though the mechanistic links to autoimmune pathology are understudied for these viruses.

Despite strong links between viruses (EBV in particular) and MS pathology, the vast majority of people infected with these viruses in their life do not go on to develop MS. This demonstrates that while infection may be necessary to trigger MS, it is not sufficient on its own to induce disease pathology. Instead, there are likely numerous additional genetic, immunological, and environmental cofactors contributing to MS disease initiation and progression.

At this time, additional research is needed to better understand the mechanistic links between viral infection and the pathologies driving disease in people with MS. Without developing this understanding, attempts to modulate MS pathologies with antivirals or vaccines will remain difficult and risky. By elucidating these mechanisms, we can open the door to new and better therapies in the future.

Description of Concept:

This initiative will support pilot projects that:

- (1) Address knowledge gaps around how viruses can lead to the initiation of MS
- (2) Study how viral infections and antiviral responses exacerbate autoimmune responses in MS

This will be accomplished through a one-year pilot research grant style mechanism, with a budget maximum of \$100,000 (direct costs). Preliminary data is not explicitly required for this initiative. Instead, this funding can be used to generate preliminary data, which in turn can be leveraged for a future research grant application. Project proposals can include creating innovative tools and demonstrating the feasibility of new approaches to address these knowledge gaps. Project proposals can also include leveraging existing datasets to study the role of viruses in MS initiation and pathology. Ultimately, projects are expected to help open novel areas of research into the links between viruses and MS.

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

- Assessment of how viral immune responses affect neuroinflammation and demyelination in MS
- Analysis of immune cell modulation driven by an active or latent viral infection
- The impact of viral infection on demyelination or nervous system repair
- Evaluation of anti-viral strategies on the pathologies and progression of MS
- Characterization of novel preclinical models of neuroinflammation with a viral component
- Feasibility study of potential approaches for an EBV vaccine trial
- Analysis of high-dimensional data sets to characterize viral-driven effects in neuroinflammation

Areas NOT supported by this RFA include:

- High throughput screens of viral sequences or peptides associated with disease onset or relapse
- Studies of JCV or DMT-induced PML
- Studies of COVID-associated exacerbation of MS disease pathologies
- Studies focusing on viral biology or lifecycle without connection to MS disease pathogenicity
- Incremental extensions of ongoing research projects without new methods or approaches

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 \$100,000 USD direct costs for up to 12 months of support will be provided and must be justified based on the scientific work plan.

Important dates:

- Pre-applications will be accepted beginning: **March 21, 2023**
- Final date for acceptance of pre-applications: **May 10, 2023 | 5:00 pm Eastern Time**
- Final date for receipt of full applications: **May 17, 2023 | 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 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?
- **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 are encouraged to contact Society scientific staff for clarification of any issues or questions regarding this RFA.

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