REQUEST FOR PROPOSALS

Therapeutic Approaches

Gene and Cell Therapy Strategies for Myhre Syndrome

May 3rd, 2024

The Myhre Syndrome Foundation (MSF) is pleased to announce a Request for Proposal (RFP) for high-impact research on prime gene editing strategies or cell therapy to address the increase in SMAD4 activity. Proposals will be accepted for Team Science Awards, which are defined as collaborative research amongst investigators with experience in gene-editing strategies or cell therapy in or outside the Myhre syndrome (MS) field.

Myhre syndrome

Myhre syndrome is a rare genetic disorder caused by two loci of missense mutations in the SMAD4 gene, which plays a crucial role in various cellular pathways such as TGF-β, PTH1R, Wnt / Beta-Catenin, Notch, or BMP.

Individuals with Myhre syndrome typically exhibit a distinctive and heterogeneous set of features, including short stature, fibrosis leading to hearing loss, gastrointestinal and respiratory pathology, aortopathy, also cardiac Muscular and skeletal abnormalities, developmental delays, and IDD.

The Myhre Syndrome Foundation

The Myhre Syndrome Foundation is a patient advocacy organization dedicated to providing hope and improving the lives of those impacted by Myhre syndrome. We foster collaboration among all relevant stakeholders to build a strong, global community in order to advance research, as well as support, educate and advocate for those impacted by Myhre syndrome.

OBJECTIVE AND AREAS OF INTEREST

The objective of this RFP is to identify promising gene and cell therapies that have the potential to dramatically reduce pathologic burden in MS patients. Potential areas of interest include:

- **Gene Editing**

  MS-identified pathogenic variants are limited to missense single nucleotide mutations SMAD4 I500V/T/M/L and R496C. MS is autosomal dominant, usually de novo, with a gain of function. Haploinsufficiency and loss of function of SMAD4 are highly pathogenic and push for a gene-editing therapeutic approach. Proposals using prime gene editing strategies would be preferred.

- **Fibrosis Cell/Gene therapy**
  Fibroproliferative reactivity is one of the threats and burdens of MS patients, and efficient therapeutic options in anti-fibrosis remain a major challenge for the treatment of MS. Proposals aimed at developing innovative therapeutics, other than the use of small molecules capable of meeting these challenges are of significant interest.

KEY SELECTION CRITERIA

- Innovative and transformative research: Novel non-small molecule approaches with a strong scientific rationale that could advance the development of a therapeutic strategy to 'cure' the disease or address fibrosis.
- Experience in prime gene editing or gene editing and cell therapy.
- Potential for rapid progression to clinical testing: Proposals that articulate a clear path to Myhre syndrome clinical application will be strongly favored.
- Scientific merit: Outstanding and rigorous proposals as determined by peer review.
- Proposals with the ability to produce therapeutic material to perform in vivo testing in mammal animal models would be preferred.

TEAM SCIENCE AWARD

Awards for team science are designed to foster a collaborative research process amongst researchers with complementary expertise and capabilities, who will work together to advance new therapeutic solutions for MS. For multidisciplinary teams of two or more Principal Investigators (PIs), MS expects to provide up to $ 450,000 over 3 years per team to undertake projects with a clear potential to lead to gene therapies or cell therapy for MS patients.

Teams may consist of investigators from the same institution or different institutions, including international ones. The designated Administrative PI is responsible for administrative leadership. All PIs on the team share authority for scientific leadership.

APPLICANT ELIGIBILITY

PIs must hold a full-time faculty or industry appointment at the level of Assistant Professor (or equivalent) or above at an academic, non-profit research institution or industry organization whose primary mission is medical research within or outside the United States. PIs must be able to show clear evidence of an independent research program. Fellows or those in other training or research support positions are not eligible.

Investigators must be specifically trained in and have documented experience with gene or cell therapy. Researchers who are new to MS are encouraged to apply but strongly advised to consult closely with an MS research expert.

Multiple applications will be accepted from a single institution, provided each application has a different PI and represents a distinct hypothesis.

Applications from PIs who do not meet the eligibility criteria will not be reviewed. If you have any questions about eligibility, please contact MSF before applying.

APPLICATION INSTRUCTIONS

There will be a two-stage peer-review application process:

1. In the first stage, Letters of Intent (LOIs) are due by July 1st, 2024. Please send to kwears@myhresyndrome.org

2. MSF will select LOIs to advance and notify applicants of their application status by July 8th, 2024. For those applications selected to advance, full-length proposals will be due by September 2nd, 2024.

All applications are due by 5:00 PM Eastern Time on the dates specified above. LOIs and full proposals received after the applicable deadline will not be considered.

Letter of Intent

All applicants must submit an LOI to MSF. Only select applicants will subsequently submit a full proposal. The LOI application consists of the following components.

1. **Title Page:** Enter the project title.

2. **Applicant/PI Information:** Team Science applications must identify one PI for administrative purposes (the Administrative PI for the proposal). This is the 'Applicant'.

3. **Organization/Institution Information:** This is the Administrative PI's institution.

4. **Key Personnel Information:** Identify all individuals who will contribute in a substantive, meaningful way to the scientific development or execution of the project, whether or not salaries are requested.

5. **Description of the scientific aims** and translational potential (max 1,000 characters).

6. **Nature of and rationale** for the proposed collaboration, the specific role of each participant, and synergistic opportunities (max 1,000 characters).

7. **Methods** (max 3,000 characters.)

8. **Past experience** of the team relevant to the project's methods and goal (max 1,000 characters)

Full-length Application

Full-length applications will be invited from meritorious LOIs selected by MSF. Applications include the following steps and components.

1. **Title Page:** Enter the project title. For proposals involving multiple institutions, please include the total amount requested for each institution in the designated spaces provided.

2. **Templates and Instructions:** Download RFP and templates.

3. **Applicant/PI:** Key information about the applicant PI. This must be the Administrative PI on team science applications.

4. **Organization/Institution:** Key information about the Applicant/PI's institution, including the name and email address of the signing official who, in addition to the PI, will be contacted if the award is selected for funding.

5. **Key Personnel:** List and provide contact information for key persons. Include all PIs on the proposal as well as any additional key personnel.

6. **Abstracts and Keywords:** Provide a lay audience friendly abstract and a technical abstract (2,000 characters maximum each) and key words. Please note: the lay abstract will become public if the award is selected for funding; therefore, it should not contain any proprietary information.

7. **Budget Period Detail:** Enter the budget detail for each award period requested. MSF will not support indirect costs, overhead costs, or other similar institutional levies in excess of 5% of the total award amount. Fringe benefits for personnel salaries are allowable.

8. **Budget Summary and Justification:** A summary of the budget detail will be shown. In addition, the budget will provide sufficient detail to evaluate the major portions of the budget that are being requested.

9. **Upload Attachments:** Upload the following:
    a. **Curriculum vitae for PIs and other key personnel:** Applicants may use the template provided or the NIH biosketch format.

    b. **Current and pending research support for the PIs,** which includes a statement of overlap. Any overlap of current or pending support with the MSF proposal must be described and explained.

    c. **Project description:** Must be formatted in Arial 11-point or Times New Roman 12-point font with no less than ½ inch margins. 5 pages maximum, inclusive of the following: Background and specific aims, preliminary data, timeline, milestones, experimental design and methods, figures (which may be embedded within the above sections), and rationale/fit with key criteria, including the potential for clinical impact. Descriptions exceeding the 5-page limit will not be considered.

    d. **Literature references:** A list of up to 20 references (maximum) supporting the project description is allowed, in addition to the 5-page project description.

    e. **For multi-institutional proposals:** Attach a letter from the Administrative PI's institution confirming that if the award is made, the institution will execute the necessary subaward agreements within 30 days of execution of the award agreement between MSF and the applicant institution and will transfer funds from their institution to the collaborating institution(s).

10. **Validate:** Check for any missing required information.

11. **Signature pages:** Print the signature page, which must be signed by the PI and the institution's signing official and uploaded as part of the application package.

12. **Submit:** Please note that no proposals will be able to be submitted past the deadline. Technical support for the online application system is not available after 5:00 PM Eastern Time.

TIMELINE

Activity	Date*
Letter of Intent	July 1, 2024
Teams of selected LOIs invited to submit full length proposals	July 8, 2024
Full length proposal due	Sept 2, 2024
Peer and organizational reviews/modifications of submissions	Oct 14, 2024
Award letters/negotiate research agreements	Oct 28, 2024
Projects commence	Nov 11, 2024

*Please note that dates are subject to change

REVIEW MECHANISM

All proposals will undergo rigorous peer review by MSF, comprised of experts in the MS field and diverse areas of gene therapy research. Applications will be scored according to the Key Selection Criteria (page 2, above). MSF will provide summaries of reviewer critiques or evaluations to applicants. Depending on peer review and MSF program priorities, MSF may work with applicants to modify the submitted work plan and/or budget prior to award execution.