# Myhre Syndrome Foundation

# Research Roadmap 2024–2029

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The MSF Research Roadmap is a patient and family-led effort that sets out our research goals over the next five years.

## Process

**The MSF Research Roadmap was devised following consultation with patients and families via surveys and focus groups, as well as industry experts, and including members of the MSF Professional Advisory Board.**

## Purpose

**The Research Roadmap is intended to be a tool for MSF to:**

- Direct our limited financial resources for research that achieves life-improving treatments as quickly and efficiently as possible, while working towards our longer-term goal of finding a cure.
- Focus on research programs that are aligned with patient, family, doctor and researcher priorities and that have measurable research endpoints.
- Incentivize international researchers to work collaboratively.

## Plan

**Our research goals focus on:**

- Basic research to determine the mechanisms at a cellular level responsible for manifestations of Myhre syndrome.
- Establishing and characterizing human cell lines for Myhre syndrome to enable drug discovery and therapeutics.
- Identifying and testing potential therapies utilizing animal models, in preparation for clinical trials. These preclinical models will be assessed for rigor and adherence to best practices for preclinical studies.
- Facilitating patient data collection and analysis through each life stage.
- Facilitating the expansion of Myhre Clinics (two pilot clinics to be identified).

**All of the goals meet the needs set out by the Myhre community to research cardiovascular complications, fibrosis and scar tissue response, and drug-repurposing opportunities.**

# Research Goal

## Basic research to determine the mechanisms at a cellular level responsible for symptoms; this will include biomarkers.

*This research priority will complement and build-on the existing Myhre animal models already in progress, and the future development of human biomarkers and cell lines.*

| Outputs expected: | Stage: | Timeline: | Cost: |
|---|---|---|---|
| Understand the mechanism(s) of the gain-of-function pathogenic variants in SMAD4 that cause Myhre syndrome.<br><br>This will include: | | 2-4 years | Cost: $200-500k |
| Cellular biomarkers identified. | In Progress<br>**1. Initiating** | | |
| Animal models developed to a stable population to be shared for external research and new potential avenues of funding. | In Progress<br>**2. Executing** | | |

***Definition of Progress Stages:*** **1. Initiating 2. Executing 3. Closing**

### Community Explanation

**Study what happens at a cellular level that cause the physical symptoms we see in Myhre.**

This research priority will include identifying phenotypes (how the syndrome presents itself, i.e. short stature, thickened skin) and biomarkers (biological measures that are relevant to Myhre syndrome, for example, high blood pressure, skin elasticity, or differing levels of proteins).

# Research Goal

## Establish and characterize human cell lines for Myhre syndrome to enable drug discovery and therapeutics.

| Outputs expected: | Stage: | Timeline: | Cost: |
|---|---|---|---|
| Create fibroblasts and lymphoblastoid cell lines (LCL). | Planning | 1-2 years | $20,000 |
| Create two induced pluripotent stem cell lines (iPSCs). This would initially include the two most common variants of Myhre syndrome that are located on the SMAD4 gene at position 496 and 500. | Planning | 1-2 years | $50,000 |

***Definition of Progress Stages:*** **1. Initiating 2. Executing 3. Closing**

### Community Explanation

**Myhre syndrome tissue and blood samples will be used to create tissue, blood and iPSC cell lines.**

iPSC cell lines are when Myhre tissues are made and grown in a laboratory that will allow researchers to understand the effects of Myhre at a molecular level and test drugs to identify potential treatments.

# Research Goal

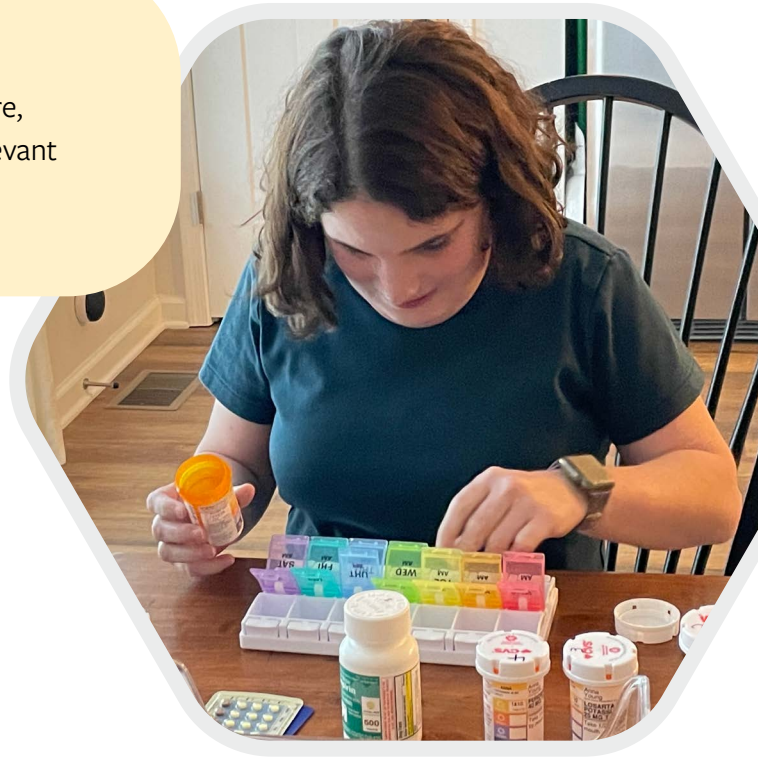
Identify and test potential therapies utilizing animal models, in preparation for clinical trials. These preclinical models will be assessed for rigor and adherence to best practices for preclinical studies.

| Outputs expected: | Stage: | Timeline: | Cost: |
|---|---|---|---|
| Determine drug repurposing potential (e.g. Losartan) and suitability for clinical trial. | In Progress **1. Initiating** | 1-2 years | $100,000 |
| Identify and test at least one drug/therapy on the models to identify suitability for clinical trial. | Planning | 2-5 years | $1m+ |
| Identify and test treatment options including suitability of gene editing, antisense oligonucleotide (ASO) and other RNA therapies. | Planning | 5-8 years | $2m |

***Definition of Progress Stages:*** **1. Initiating 2. Executing 3. Closing**

## Community Explanation

Using the information on the basic biology of Myhre, we will move forward with the identification of relevant treatment options in readiness for clinical trials.



# Research Goal

## Facilitate patient data collection and analysis through each life stage.

| Outputs expected: | Stage: | Timeline: | Cost: |
|---|---|---|---|
| Facilitate the analysis of patient data that gathers retrospective, cross-sectional and progressive data to be utilized for research and preparation for clinical trial readiness.<br><br>Identification of genotype-phenotype relationships and physiologic biomarkers. | In Progress<br>**2. Executing** | 1-2 years | $50-75k |

***Definition of Progress Stages:*** **1. Initiating 2. Executing 3. Closing**


### Community Explanation

This research priority means that MSF is collecting data on Myhre patients, to track more effectively how Myhre is presenting at every stage of life.

# Research Goal

## Facilitate the expansion of Myhre Syndrome Clinics (two pilot clinics to be identified).

| Outputs expected: | Stage: | Timeline: | Cost: |
|---|---|---|---|
| Contribution to patient data collection and analysis on Myhre syndrome.<br><br>Increase dedicated resources in multiple locations.<br><br>Increase the number of Myhre patients seen by a Myhre syndrome specialist (who has seen multiple Myhre patients, contributes to Myhre research). | Planning | 2-3 years | $100-200k |

***Definition of Progress Stages:*** **1. Initiating 2. Executing 3. Closing**

### Community explanation

MSF wants to expand collaboration by increasing the number of Myhre Clinics, with two pilot clinics identified. The creation of Myhre clinics will provide better support and resources for Myhre patients.

# Summarized feedback from Myhre Community Focus Groups & Surveys

## Cardiovascular Complications - Top Priority

The Myhre community indicated that the cardiovascular complications (congenital and acquired) were of primary concern for research.

## Fibrosis & Scar Tissue - Understanding the way the body behaves

The Myhre community wants to understand why the body stiffens over time or at point of trauma (i.e. an injury or intubation). Fibrosis affects so many of the body systems, the community wants research to understand what is happening at a cellular level to create this fibrosis response.

A common concern is that excessive scar tissue forms during the process of healing after surgeries and other medical interventions. The community recognizes that sometimes surgery is unavoidable, but research is needed to understand the scar tissue response.

## Drug Repurposing

After a pilot pre-clinical trial was undertaken for Losartan (a blood pressure drug), many community members discussed Losartan and a need to progress the study to test effectiveness, as the initial study was only in four people.

## Cognitive and Behavioral Concerns*

Parents talked about concern for their children at school and social settings and how to assist them as they grow up. Key discussion in the focus groups included making friends and integrating into society so their children have meaningful relationships.

## Support for Long Term Planning*

Planning for the future and putting strategies in place to make sure adults with Myhre have the care they need is a key priority. Many parents cited concerns for what would happen to their children when they are no longer here.

**These areas of need will be supported by the MSF Patient Advocacy Committee.*

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