Novel Prognostic Tissue and Blood Biomarkers of Systemic Sclerosis to aid future Drug Development (PrognoSScis)

UNMET MEDICAL NEED

Scleroderma is a chronic connective tissue disease generally classified as an autoimmune disease. This disease causes inflammation in the skin and other areas of the body. The inflammation associated with Scleroderma triggers the body's own immune system to make too much collagen, leading to the hardening and tightening of the skin and connective tissues, including scar tissue (fibrosis).[1] Scleroderma can also extend beyond the skin, and when this occurs it is called Systemic Sclerosis (SSc). For SSc patients the complications can result in damage to the heart, lungs, kidneys and the digestive system. As the tissues of these affected organs become hard and fibrous, they function less efficiently having a substantial impact on morbidity, mortality and the quality of life for patients.

In the United States approximately 300,000 individuals have Scleroderma with 1/3 of these patients having the SSc form. Women are mostly affected by Scleroderma representing 80% of the patients living with the disease. While the disease can occur in all genders, ages, races and ethnic groups, it usually occurs between the ages of 30 and 50 and can affect African Americans more severely.[2]

SSc has the highest rate of fatality of any rheumatic disease and is one of the last high unmet need areas in Rheumatology. It is also a complex disease that can progress in variable ways in individual patients. This heterogeneity can make both disease definition and diagnosis difficult. At present not enough information is known regarding the SSC molecular taxonomy to deliver the right therapy to the right patients at the right time. There is a significant unmet need for biomarkers to help subtype patients and better understand the pathogenic pathways, to help improve clinical trials and ultimately patient care by providing the understanding and tools for a tailored, precision medicine approach.

PROJECT OBJECTIVE

This project aims to discover novel prognostic molecular biomarkers to provide information on the likely natural course of Systemic Sclerosis (SSc) in a patient on standard of care treatments and better inform on the rate of progression of organ-specific disease such as interstitial lung disease and skin fibrosis. By further discerning the heterogeneity among this patient population it will enable better patient stratification for clinical trials and the likelihood of response to targeted therapeutics, ultimately improving patient outcomes and opportunities for more tailored and effective treatment options.

BACKGROUND

To date, there are no approved therapies for overall SSc, although the US Food and Drug Administration (FDA) has approved both nintedanib and tocilizumab for SSc-associated interstitial lung disease (ILD). However, the current medical therapies are minimally effective as they are directed towards managing complications and providing symptomatic relief. Recent trials have highlighted the difficulty in SSc trial design and the need to be able to better stratify the heterogeneity that exists in the patient populations and outcome measures. While targeted therapies are emerging, biomarkers for sub-stratifying patients based on individual profiles are lacking.

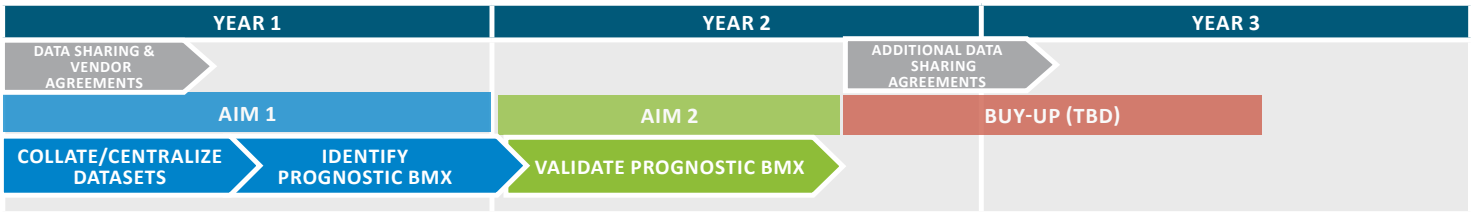
Clinicians have used Scleroderma specific autoantibodies to help classify those at risk of progressive lung fibrosis versus scleroderma renal crisis. In addition, recent data suggest that patients can be classified using skin and blood gene expression profiling.[3] Preliminary observations by multiple groups including The University of Michigan and Whitfield Laboratory at Geisel School of Medicine at Dartmouth suggest that additional biological markers for discerning these different biological phenotypes are critical to move the field forward and reduce the heterogeneity observed in different SSc clinical trials. The FNIH Biomarkers Consortium has developed this project that will facilitate targeted therapy, tailored to the distinct patient subtypes and improve long-term healthcare outcomes and the quality of life of SSc patients worldwide.

PROJECT AIMS

This two-year project includes the following Aims:

Aim 1: Identify blood-based and tissue biomarkers in patients with early SSc involvement, with and without ILD, to predict outcomes and a reliable clinical course (i.e., skin/lung progression,

PROJECT TIMELINE



PROs, and composite endpoints, etc.).

- Establish a unique dataset of retrospective patient cohorts and data from industry and academia to support the appropriately powered studies in Aim 1 and Aim 2.
- Perform multi-dimensional, molecular characterization of disease spectrum to better define and understand disease heterogeneity in diverse SSc and ILD clinical subtypes.

Aim 2: Validate prognostic biomarkers identified in Aim 1 that correlate with clinical subtypes, predict poor outcomes and trial endpoints, while accounting for background immunosuppressive therapy.

**Parallel Activity: Develop consensus white paper on key domains and a core-set of outcome measures for future SSc clinical trials for a publication.*

Ideally, the study population will include adult SSc patients with a focus on skin involvement and ILD that participated in clinical trials. The project believes the advantages of using clinical trial data for these initial aims will ensure that the patient group is homogeneous, and the data is of high quality- accurate, reliable, and complete. Additionally, all patient samples used in this project will be classified according to the accepted ACR/EULAR 2013 Classification Criteria for Systemic Sclerosis. Note, these are preliminary criteria and could be modified based on recommendations by the Project Team.

A buy-up opportunity or future study pending the success of this project will be to identify prospective cohorts (on-going or future trials from large prospective studies and registries) to validate findings.

OPPORTUNITIES FOR INVOLVEMENT

The Foundation for the National Institutes of Health (FNIH) is actively seeking private-sector participation in this Project. A total of $3,713,184 in private funds over two and a half years is required to fully support the project. The below chart outlines the contributions necessary for participation as a full-funding partner. Financial support at other levels and in-kind contributions are also welcome.

ORG SECTOR	TOTAL CONTRIBUTION PAYABLE OVER 2.5 YEARS
Industry	$600,000
Non-Profits	$200,000

Funding partners may have multiple participants on the Project Team, and full-funding partners may cast one vote on project decisions. Throughout the life of the project, the FNIH will work to ensure that all partners have ample opportunity to provide input and share valuable expertise and receive broad acknowledgment for being a scientific and funding partner. The FNIH aims to secure funding commitments in Q3/Q4 2023. This will enable private partners' active involvement in the immediate next steps of the process and ensure that project activities can begin in Q4 2023/Q1 2024.

REFERENCES

1. Scleroderma Research Foundation https://srfcure.org/living-with-scleroderma/about-scleroderma/
2. National Scleroderma Foundation https://scleroderma.org/who-gets-scleroderma/
3. Khanna D, Denton CP. Evidence-based management of rapidly progressing systemic sclerosis. Best Pract Res Clin Rheumatol. 2010;24(3):387-400. doi:10.1016/j.berh.2009.12.002

PROJECT IMPACT

- **An unprecedented dataset for developing a deep understanding of the clinical, serological and immunologic heterogeneity of SSc patients by applying proteomic and transcriptomic technologies to skin, lung and matched blood samples**
- **Develop information that will lead to a white paper and potential further FDA Guidance for SSc**
- **Potential approval of novel prognostic biomarkers through the Biomarker Qualifications program**

Benefits to Industry and Physicians
- Support development of SSc medications and reduce overall in healthcare spending
- Improve clinical trial outcomes and targeted therapy approaches or "precision medicine"

Regulatory Advantages
- Develop information that will lead to a white paper and potential further FDA Guidance for SSc
- Approve a novel prognostic biomarkers through the Biomarker Qualifications program

Benefits to Patients
- Establish accurate prognosis of SSc
- Allow for more effective drug development trials and personalized treatment and for SSc patients

To learn more about becoming a scientific and funding partner in the PrognoSScis Project, please contact:

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