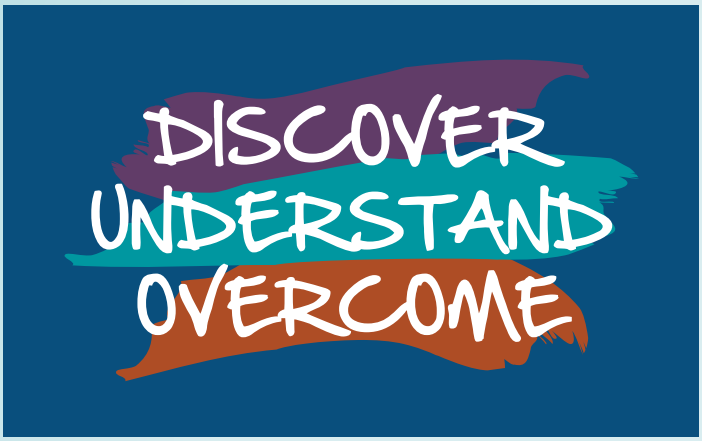
Scleroderma Foundation 2021 Research Grant Awards



The Scleroderma Foundation is a leader in the effort to **discover** the cause, **understand** the mechanism, and **overcome** the symptoms of scleroderma through its **Peer-Review Research Grant Program** that ensures scientific merit is the determining factor in making awards. A panel of independent scientists reviews proposals annually and assigns scores for project design and quality of science with the same merit-based system utilized by the National Institutes of Health (NIH).

Awards are granted in two categories. **New Investigator Awards** are three-year grants for scientists entering the field of scleroderma research. The intent is to provide an opportunity to test theories and develop data that then form the basis of a larger NIH grant application. **Established Investigator Awards** are two-year grants given to scientists with a history of studying scleroderma. The funding provides an opportunity to pursue innovative ideas.

Eight new research grants totaling **$1.2 million** were awarded for 2021. Because grants are spread over two or three years, in any given year, the Foundation has funding commitments to some 18 ongoing projects. Our commitment to these projects drive fundraising efforts such as *Stepping Out to Cure Scleroderma* walks.

Three awards were given in honor of remarkable individuals who made significant contributions to the scleroderma community.

2021 Grant Awards

The Scleroderma Foundation proudly announces the eight 2021 grants. These projects received the Peer-Review committee's highest ranking for scientific design quality and the prospect of advancing the scleroderma body of knowledge.

The Marta Marx Fund for the Eradication of Scleroderma

IDO AMIT, PH.D.
Weizmann Institute of Science

Established Investigator,
Two-Year Award

Comprehensive Single Cell Analysis of Skin and Blood of Scleroderma Patients: Towards Identification of Disease Molecular Mechanisms, Prognostic Biomarkers and Potential Therapeutic Targets.

Systemic sclerosis (SSc) is rare autoimmune disease with high morbidity and mortality, characterized by excessive production and accumulation of collagen (fibrosis) in the skin and internal organs, injuries to small arteries, and overactivation of immune system. There are still many unmet needs in SSc; the triggering events linked with disease development, the specific cells, genes, and pathways leading to SSc are still only very partially understood. The incomplete understanding of SSc and the lack of biomarkers that identify patients at high risk for complications limit the possibilities of development of effective treatments. Single-cell genomic technologies, many of which we pioneered, provide a unique technology and opportunity for better understanding of the mechanisms leading to the pathology of SSc. We will apply the MARS-seq technology that we recently developed, for detecting rare cell populations in the skin and blood of individual SSc patients to characterize their cellular and molecular phenotype in much greater resolution then possible before. Our study holds great potential to provide clinicians with new and powerful molecular tools for understanding the cells involved in SSc, for finding new biomarkers that have great potential for early disease detection and prediction of SSc complications, and for tailoring and identifying new therapeutic targets.

Mark Flapan Award

JONATHAN A. GARLICK, D.D.S., PH.D.
Tufts University School of Dental Medicine

Established Investigator,
Two-Year Award

Functional Analysis of Cellular Diversity and Cell-Cell Interactions in Scleroderma 3D Skin-Like Tissues

The goal of our research is to create skin in our lab ("lab-grown skin") using cells from people with scleroderma to understand how similar lab-grown skin is to the actual skin of the people these cells were taken from. Most research using cells from people with scleroderma is studied as a single layer on plastic dishes that do not recreate complex tissues affected in scleroderma. As a first step to overcome this limitation, the Garlick and Whitfield labs have recently shown that lab-grown skin shows key features of scleroderma with two cell types. In this new research, we will use additional cell types to see if we can make lab-grown skin that recreates scleroderma that is distinctive for specific patients. We will first figure out how to best grow lab-made skin with four different cell types, which recreates key features of scleroderma. We will study how these cells communicate with each other to cause scleroderma. We will collaborate with the Whitfield lab at Dartmouth to do genomic analyses that can identify novel subsets of scleroderma to see how lab-grown skin compares to skin taken from people with scleroderma. We expect our results to help us and other researchers use lab-grown skin to better understand how scleroderma develops and to test new drugs to treat scleroderma.

Walter & Marie Coyle Research Grant

HANS DOOMS, PH.D.
Boston University

Established Investigator,
Two-Year Award

Functional Characterization of Aberrant PD-1+TIGIT+T Cell Subsets Expanded in Systemic Sclerosis Patients

Scleroderma is an autoimmune connective tissue disorder associated with fibrosis of the skin and internal organs. There is evidence that an aberrant immune response drives much of the pathogenesis of this disease. Co-inhibitory receptors such as CTLA-4 and PD-1 are mechanisms to control autoimmune responses. However, these receptors are also expressed on dysfunctional T cells that emerge during chronic immune activation. We discovered that in scleroderma, patients' immune cells carry increased levels of multiple co-inhibitory receptors on their surface. T cells subsets that co-express the PD-1 and TIGIT receptors are particularly enriched in blood from scleroderma patients. We therefore propose to investigate the role of PD-1+TIGIT+ T cells from scleroderma patients in the faulty activation of fibroblasts and endothelial cells that leads to fibrosis and microvascular damage. We hypothesize that PD-1+TIGIT+ T cells from scleroderma patients have lost their anti-fibrotic activities due to dysregulated cytokine production, thus enabling fibrosis. To test this we will co-culture PD-1+TIGIT+ T cells with fibroblasts and endothelial cells and define the changes in T cell and target cell functions. A successful outcome of this study will provide a rationale for therapeutically targeting PD-1+TIGIT+ T cells in scleroderma.

HARRY KARMOUTY-QUINTANA, PH.D.
University of Texas Health Science Center at Houston

Established Investigator,
Two-Year Award

The Role of SIX1 in SSc-ILD

A serious and life-threatening complication of scleroderma is the development of lung fibrosis. In lung fibrosis, scar tissue in the lungs prevents oxygen from reaching the red blood cells that distribute oxygen to the body. Unfortunately, we do not understand why scarring develops in lung fibrosis. Scientists believe that fibroblasts (a cell type that is responsible for wound healing) become over-reactive and do not stop trying to repair the lung. This results in a disorganized repair process that makes it much more difficult for oxygen to reach the red blood cells in the lung. We think that a gene called SIX1 that works together with another gene called EYA2 are responsible for making the fibroblast over-reactive. To understand this process, we will use methods that aim to identify what these fibroblasts are producing. Then we will use methods where our target genes (SIX1 and EYA2) are genetically removed from fibroblasts and test if this can stop the scarring of the lung. If our idea is correct, our research can lead to the discovery of new medicines that can stop lung fibrosis, improving the lives of people with scleroderma that develop lung fibrosis, a common and serious complication.

MENGQI HUANG, PH.D.
University of Pittsburgh

New Investigator,
Three-Year Award

Investigation of Disease Associated Skin Endothelial Cells in Systemic Sclerosis Using Single-Cell Transcriptomics and Epigenomes

Despite progress in treating the symptoms of vascular disease in SSc, the underlying mechanisms remain poorly understood. An improved knowledge of the molecular and cellular pathways that contribute to SSc vasculopathy could help in the design of effective therapies in the future. Studies of vascular disease have been challenging due to the relative inaccessibility, and difficulty isolating and culturing of endothelial cells (ECs) in vitro without altering their genetic and epigenetic features. Emerging technology of single-cell sequencing allows studies with limited numbers of primary cells from human tissues, helping to identify genetic and chromatin structures of an aberrant EC population that is specific to SSc patients. Further study of the SSc ECs will lead to discoveries of the key genes and proteins that regulate the disease-associated phenotypes in the injured ECs, and help in the development of SSc-EC directed therapies.

KIMBERLY SHOWALTER, M.D., M.S.
Hospital for Special Surgery

New Investigator,
Three-Year Award

Dermal Fibroblast Immunophenotype to Predict Clinical Trajectory in Early and Late Diffuse Systemic Sclerosis

Scleroderma is a complex autoimmune condition for which treatment options are limited and have toxic effects. The purpose of this study is to determine if skin biopsy assessments of fibroblasts, a key cell involved in scleroderma, can predict clinical improvement one year later. We will first analyze data collected during three early scleroderma clinical trials to determine if baseline fibroblast phenotype (measured by two biopsy stains and a gene expression signature of fibroblast inflammation) predicts clinical improvement one year later. We believe that individuals with inflamed fibroblasts will respond best to anti-inflammatory treatments. Next, we will study fibroblasts in late scleroderma, when treatments are usually less effective, and test if fibroblast features can predict clinical outcomes later in disease. The natural history of untreated late scleroderma is that skin improves; however, some patients continue to struggle with uncomfortable, tight, and thickened skin. If successful, we will have created a tool to predict who will respond to treatment in early disease and who will likely improve without treatment in later disease. This can help ensure that treatments are offered to those patients likely to benefit and conversely, that patients unlikely to benefit from potentially toxic treatments may be spared that exposure.

STEPHANIE STANFORD, PH.D.
University of California, San Diego

New Investigator,
Three-Year Award

LCM-RNAseq for Topological Mapping of Scleroderma Skin Pathology

This project is relevant for developing personalized treatments for scleroderma. Scleroderma is a chronic autoimmune disease characterized by hardening of the skin and internal organs—called fibrosis—caused by excessive collagen production. There are no FDA-approved medications for scleroderma, and it is often lethal. The damage that occurs in the skin during scleroderma is variable among patients and even in different skin regions of the same patient. Understanding the individual scleroderma patient skin environment will be beneficial for developing scleroderma therapies and identifying markers in the skin that can be used for predicting response to treatment. This award will impact patients by providing a method called laser capture microdissection-RNA sequencing to analyze changes that occur in small regions of scleroderma patient skin. We hypothesize that blood vessels in the skin of scleroderma patients send signals to nearby cells that cause them to produce excessive collagen. Using skin from scleroderma patients, we will apply our newly established method to characterize the disease promoting signals in the skin blood vessels, and the response of nearby cells in the skin. The approaches that will be used in this award are innovative and have not yet been applied to the study of scleroderma patient skin.

YAN WANG, M.D., PH.D.
Cleveland Clinic Foundation

New Investigator,
Three-Year Award

The Role of Hyaluronan and O-GlcNAcylation in Fibroblast Turnover and Function in Scleroderma

The mechanism how scleroderma develops is poorly understood and the efficacy of current treatment is unsatisfactory. This study proposes to investigate the pathology of scleroderma from a new angle—focusing on two pathways involving sugar molecules: hyaluronan (HA) synthesis and protein O-GlcNAcylation. HA is a large sugar molecule that is essential for both normal physiology processes such as tissue injury and repair and development of diseases such as cancer progression. Abnormally high levels of HA in skin and blood of scleroderma patients has been reported but whether the abnormal HA level is responsible for the development of scleroderma remains unclear. Protein O-GlcNAcylation is the addition of a sugar molecule, O-linked β-N-acetylglucosamine (O-GlcNAc), to certain sites on the proteins. Abnormal level of O-GlcNAc has a crucial role in the onset of various chronic diseases including diabetes, cancer, and Alzheimer's. However, whether an abnormal level of O-GlcNAc gives rise to the development of scleroderma remains unknown. We hypothesize that increased HA content and abnormal level of O-GlcNAc lead to increased fibrosis in scleroderma. Further, inhibition of HA and/or O-GlcNAc pathways can work as new therapeutic strategies for scleroderma treatment. To test the hypothesis, we will try to get rid of either HA or O-GlcNAc in mouse skin and see if this will reverse the skin fibrosis induced by bleomycin injection, which is a well-accepted mouse model to study scleroderma. In addition, we will investigate underpinning molecular mechanism by studying primary skin cells isolated from mouse skin and cultured in petri dishes. The proposed study is novel since scleroderma has not been studied from this new "sugar-related" angle. The findings from this research will obtain new insights in understanding the basic mechanism of scleroderma and finding new therapeutic targets.

The Marta Marx Fund For the Eradication of Scleroderma

In 2000, the late **Rudolph Juhl**, a New York stockbroker, honored his sister, **Marta Marx**, with the largest gift ever made to the Scleroderma Foundation—a $5 million bequest—to establish the *Marta Marx Fund for the Eradication of Scleroderma*. In 2002, the **Estate of Marta Marx** added $5 million to make the total $10 million. In honor of Mr. Juhl's gift, the Foundation designated the Marta Marx Fund for the Eradication of Scleroderma award to be presented to the scientist whose research proposal achieved the highest score.

The Mark Flapan Award

The Mark Flapan Award is presented annually to a scleroderma researcher whose proposal received the second highest score by the Foundation's Peer Review Committee. The award is named in honor of the late psychologist **Mark Flapan**, who had scleroderma, and whose contributions to the Foundation's publications and educational materials paved the way for increasing awareness and greater patient understanding of the disease.

The Walter & Marie Coyle Research Grant

Marie and Walter Coyle were among the founders of the Scleroderma Foundation, in addition to founding one of its predecessor organizations, the Scleroderma Federation. For more than 30 years, Walter and Marie were tireless volunteers and devoted champions for scleroderma-related causes, working almost full-time for the Foundation's New England Chapter and the national office of the organization. They both served on the national Board of Directors.

Marie is credited with being the architect of the Foundation's Peer-Review Research Program.

Upon Walter's passing in 2009, The *Walter A. Coyle Memorial Research Grant* was established. The grant was renamed to include Marie on the occasion of her retirement and in honor of her 40 years of distinguished service.