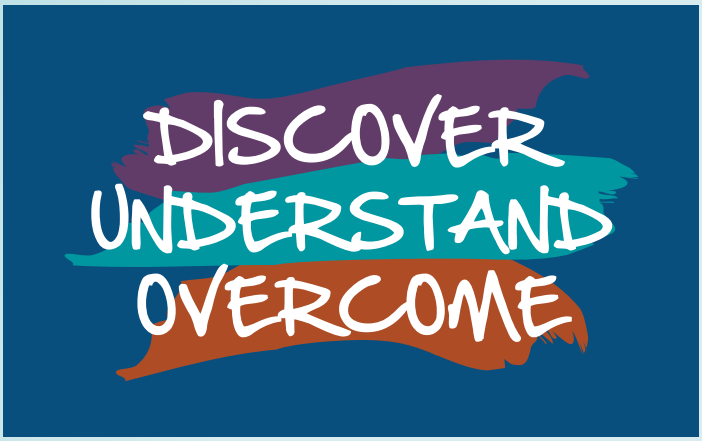
Scleroderma Foundation 2020 Research Grant Awards



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.

2020 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

BENJAMIN KORMAN, M.D.
University of Rochester

New Investigator,
Three-Year Award

Pathogenic Role of TNF-a and TNF Receptors in Experimental Scleroderma Associated Pulmonary Arterial Hypertension

Pulmonary hypertension is a severe vascular complication of scleroderma which carries significant morbidity and mortality, and whose biologic basis remains poorly understood. Research in scleroderma-associated pulmonary arterial hypertension (SSc-PAH) has been limited by a lack of animal models of this disease. We have recently shown that tumor necrosis factor (TNF) transgenic mice die early, have severely elevated heart pressures, and have multiple features which closely resemble SSc-PAH. Using this novel animal model of SSc-PAH, this application seeks to understand the how TNF may cause pulmonary hypertension. The main hypothesis proposed is that TNF has different signaling mechanisms in different cells and this leads some cells like blood vessel (endothelial) cells to die while causing other cells like smooth muscle cells and fibroblasts to proliferate. The application proposes to use cell culture, single cell RNA sequencing, and transgenic mice to understand how TNF may be acting. These experiments will provide important insights into TNF's role in driving processes which are fundamental to the development of SSc-PAH, and if successful, will provide a strong rationale for additional studies in humans both to better define this pathway and to study the use of anti-TNF treatment in patients with SSc-PAH.

Mark Flapan Award

FRANCK J. BARRAT, Ph.D.
Hospital for Special Surgery

Established Investigator,
Two-Year Award

Functional Impact of TLR7/8 Biallelism in SSc Patients

It is well documented that there is a female predominance of about 4:1 in scleroderma, and the usual age of onset is 35 – 55 years of age. Women have two X chromosome, but a process called X chromosome inactivation (XCI) makes sure in normal situations that only one of the two X chromosome is active while the other remains inactive. The observation of a female prodominance is questioning whether genes located on the X chromosome could be dysregulated in women patients and whether this could explain why the disease affects women.

This project is a collaboration between the Barrat lab in New York and the Guery lab in Toulouse and stems from two key observations in our respective laboratories. First, we recently demonstrated that a gene called TLR8 is a key player in promoting the disease, using clinical samples from scleroderma patients, but also using a mouse model of the disease (see Ah Kioon et al. Science Translational Medicine, 2018). Second, it is known that TLR8 and a related gene, TLR7, are encoded on the same locus of the X chromosome. We demonstrated that TLR7 can escape XCI in a fraction of immune cells from women, leading to the expression of two copies of that gene instead of a single copy (see Souyris et al. Science Immunology, 2018). This is interesting as the expression of two copies of either TLR7 or TLR8 is sufficient to induce autoimmunity in mice.

Our hypothesis is therefore that a dysregulation of XCI at the TLR7/8 loci may occur in female scleroderma patients, and that the presence of two copies of these genes is fueling inflammation and promoting chronic disease development. Although closely located on the X-chromosome, the regulation of TLR7 and TLR8 expression is strikingly different as these TLRs are rarely co-expressed, and whether TLR8 escapes XCI cannot be modeled based on TLR7 data alone. This hypothesis will be tested using samples from scleroderma patients and we will evaluate what are the consequences of such "double expression" on the cellular activation of blood cells in women patients. We believe that this is a very innovative hypothesis and if successful, that these experiments will tell us whether the predominance of the disease in female patients can be explained, at least partially, by a defect in XCI in the TLR7/8 genomic region.

Walter & Marie Coyle Research Grant

MARIA TROJANOWSKA, Ph.D.
Boston University

Established Investigator,
Two-Year Award

Regulation of Lymphatic System in Scleroderma

To improve treatment options for patients with scleroderma (SSc), a better understanding of the molecular and cellular mechanisms that cause the vascular defects of the disease is needed. The vasculature mediates two phases of inflammation: the leakage phase, modulated by endothelial cells, which results in edema and swelling, and the drainage phase, controlled by lymphatic endothelial cells, which clears interstitial fluid and results in resolution and return to homeostasis. Both of these systems are impaired in scleroderma patients. We propose to determine the contribution of transcriptional factors ERG and Fli1 to the phenotypic changes in SSc blood and lymphatic vasculature and functionally test how the absence of ERG and Fli1 affects the function of vascular system in scleroderma patients.

Cogan Family Research Grant

TOMOKO HAYASHIDA, M.D., Ph.D.
Ann & Robert H. Lurie Children's Hospital of Chicago

Established Investigator,
Two-Year Award

Role of Smad Anchor for Receptor Activation (SARA) in Skin Fibrosis

While accumulation of activated cells called myofibroblasts and production of scar material in skin and other organs by the myofibroblasts is the characteristic of excess scarring in

scleroderma (SSc), origin of myofibroblasts and their mode of activation are largely unknown. While our recent findings indicate that vascular pericyte is one such progenitor of myofibroblasts, and that a novel anti-fibrotic molecule called Smad Anchor Receptor Activation (SARA) prevents pericytes from becoming myofibroblasts, SARA being a scavenger protein, elucidation of molecules, function of which is regulated by SARA is essential to utilize SARA as an anti-fibrotic target. Using a mouse in which pericytes can be traced by fluorescent protein expression, we will perform an unbiased large-scale gene expression analysis to find genes that are differentially expressed in activated pericytes and are regulated by SARA, and assess whether the candidate genes found could indeed participate in SARA-mediated inhibition of pericyte activation. We will also evaluate possible association of SARA expression levels with clinical presentation and/or outcome in SSc patients.

Resulting finding will lay the groundwork for future, larger studies of novel targets for preventing and treating skin scarring.

DAVID A. FOX, M.D.
University of Michigan

Established Investigator,
Two-Year Award

Funded by the Michigan Chapter

Targeting CD13 as a novel therapeutic approach for scleroderma

Scleroderma is characterized by inflammation, scarring of the skin, and decrease in blood vessel formation throughout the body, all of which trigger potentially lethal damage to the organs. CD13 is a multi-functional cell surface molecule that is expressed on many cell types, including skin cells. Although CD13 is typically bound to cell membranes, it can be shed to become soluble form that is proinflammatory. It does so by acting on receptors on cells. In this study we plan to examine the role of soluble CD13 and its receptor in skin cells derived from scleroderma patients as well as an animal model of scleroderma. We will examine whether blocking CD13 receptors improve the disease. Our goal is to generate sufficient evidence to explore the possibility of using CD13 inhibitors as a therapeutic option for this disease.

CORY PERUGINO, D.O.
Massachusetts General Hospital

New Investigator,
Three-Year Award

Unbiased and Comprehensive Adaptive Immunophenotyping to Determine the Relevance of CD4+ Cytotoxic T Lymphocytes in the Pathogenesis of Systemic Sclerosis

Systemic sclerosis is an autoimmune chronic inflammatory disease resulting in fibrosis or scar tissue affecting multiple organs including the skin, lung, heart, intestines and kidneys. While previous research has taught us much in terms of the immune system in systemic sclerosis, we remain with unsatisfactory treatment options.

Deeper insight into the immune response is a hopeful means of identifying new treatment targets to curb the progression of this disease and improve the prognosis of patients with systemic sclerosis. In this proposal, we seek to perform comprehensive studies on the immune response in systemic sclerosis and compare this to two other autoimmune diseases marked by chronic inflammation and fibrosis. These studies will use idiopathic pulmonary fibrosis, a chronic fibrotic disease of the lungs and IgG4-related disease, an autoimmune fibrotic disorder that affects multiple organs with tumor-like masses, as disease comparisons. Based on similarities in the immune responses that we have observed across these diseases, we now aim to extend the studies further and understand both the differences and similarities in the immune responses that define these diseases. Specifically, we are focused on the identification of the main immune cell that drives fibrosis in systemic sclerosis. Ultimately, we hope that this work will lead to the development of new therapies for patients with systemic sclerosis.

CATHERINE ELIZABETH SIMPSON, M.D., M.H.S.
Johns Hopkins University

New Investigator,
Three-Year Award

The Role of Xanthine Oxidoreductase Activity and Altered Metabolism in Scleroderma-Associated Pulmonary Arterial Hypertension

Pulmonary arterial hypertension (PAH) is a devastating disease of the lungs and heart that causes heart failure and death.

PAH commonly complicates scleroderma (SSc) and is a leading cause of death in this population. Recent technologic advances have allowed researchers to identify proteins and metabolic pathways dysregulated early in SSc-PAH development that are not targeted by current PAH medications, all of which act on the same three biologic pathways that regulate late manifestations of disease. One protein implicated in PAH development in animal models is xanthine oxidoreductase (XOR). Inhibition of XOR prevents PAH from occurring in rats, however XOR inhibition has not been studied in humans with PAH.

Thus, we propose measuring XOR activity and downstream metabolic pathways in blood samples taken from patients with SSc, both with and without PAH. If we find progressive increases in XOR and altered metabolism prior to development of PAH, this will implicate XOR in influencing SSc-PAH development. If we find that levels of XOR and metabolites are significantly related to measures of PAH severity, this will implicate XOR in SSc-PAH progression.

Either finding would support future trials examining the effects of XOR inhibitors in patients with SSc-PAH.

ELEANOR VALENZI, M.D.
University of Pittsburgh

New Investigator,
Three-Year Award

Transcriptional and Epigenetic Investigation of the Master Regulator of Myofibroblast Transformation in Systemic Sclerosis-Associated Interstitial Lung Disease

Interstitial lung disease (ILD) is the leading cause of death in patients with systemic sclerosis (SSc), an autoimmune disease resulting in fibrosis of the skin, lungs, and other organs. With limited effective treatments, SSc-ILD is a devastating disease resulting in progressive breathlessness, respiratory failure, and death. Fibrosis is caused by cells, known as myofibroblasts, that produce excessive collagen, a protein that scars the lungs and skin. However, no treatments currently exist to stop these overactive cells in systemic sclerosis. Using new technology, we are now able to isolate individual cells from the lungs removed from patients with SSc-ILD at the time of lung transplant and study the RNA molecules and DNA structure encoding for proteins like collagen, as well as all active genes in the cell. This approach allows us to directly compare the RNA and DNA structure in diseased myofibroblasts with normal fibroblasts, in order to help determine which specific genes and proteins cause the diseased form, and further examine these proteins as potential drug targets.

The development of new myofibroblast-directed therapies has the promise of preventing disease progression to severe breathlessness and respiratory failure, resulting in lung transplantation or death, in patients with SSc-ILD.

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.